

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 February 2004 (19.02.2004)

PCT

(10) International Publication Number
WO 2004/014920 A1

- (51) International Patent Classification⁷: **C07D 495/04**, A61K 31/4365, A61P 19/02, 29/00, 37/02
- (74) Agent: **THOMPSON, John**; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
- (21) International Application Number:
PCT/GB2003/003501
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 11 August 2003 (11.08.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0218800.1 13 August 2002 (13.08.2002) GB
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **CELL-TECH R & D LIMITED** [GB/GB]; 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **BROOKINGS, Daniel, Christopher** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **DAVIS, Jeremy, Martin** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **LANGHAM, Barry, John** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).
- Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2004/014920 A1

(54) Title: BICYCLIC HETEROAROMATIC COMPOUNDS AS KINASE INHIBITORS

(57) Abstract: A series of 5-6 fused ring bicyclic heteroaromatic derivatives, based in particular on the 6-oxo-6,7-dihydrothieno[2,3-b]pyridine ring system, being inhibitors of p38 kinase, are accordingly of use in medicine, for example in the treatment and/or prevention of immune or inflammatory disorders.

BICYCLIC HETEROAROMATIC COMPOUNDS AS KINASE

INHIBITORS

5 This invention relates to a series of 5-6 fused ring bicyclic heteroaromatic derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

 Immune and inflammatory responses involve a variety of cell types with control and co-ordination of the various interactions occurring *via* both cell-cell
10 contacts (e.g. integrin interactions with their receptors) and by way of intercellular signalling molecules. A large number of different signalling molecules are involved including cytokines, lymphocytes, chemokines and growth factors.

 Cells respond to such intercellular signalling molecules by means of intracellular signalling mechanisms that include protein kinases, phosphatases and
15 phospholipases. There are five classes of protein kinase of which the major ones are the tyrosine kinases and the serine/threonine kinases [Hunter, T., *Methods in Enzymology (Protein Kinase Classification)*, p. 3, Hunter, T. and Sefton, B.M. eds., vol. 200, Academic Press, San Diego, 1991].

 One sub-class of serine/threonine kinases is the mitogen activating protein
20 (MAP) kinases of which there are at least three families which differ in the sequence and size of the activation loop [Adams, J. L. *et al.*, *Progress in Medicinal Chemistry*, pp. 1-60, King, F.D. and Oxford, A.W. eds., vol. 38, Elsevier Science, 2001]: the extracellular regulated kinases (ERKs); the c-Jun NH₂ terminal kinases or stress activated kinases (JNKs or SAP kinases); and the p38 kinases, which have a
25 threonine-glycine-tyrosine (TGY) activation motif. Both the JNKs and p38 MAP kinases are primarily activated by stress stimuli including, but not limited to, proinflammatory cytokines, e.g. tumour necrosis factor (TNF) and interleukin-1 (IL-1), ultraviolet light, endotoxin and chemical or osmotic shock.

 Four isoforms of p38 have been described (p38 α / β / γ / δ). The human p38 α
30 enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially termed CSAID binding protein-1 and -2 (CSBP-1 and CSBP-2 respectively) [Lee, J. C. *et al.*, *Nature (London)*, 1994, 372, 739-46]. CSBP-2 is now widely referred to as p38 α and differs

- from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons that are conserved in both mouse and human [McDonnell, P.C. *et al.*, *Genomics*, 1995, 29, 301-2]. CSBP-1 and p38 α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue
- 5 distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38 β which has 70% identity with p38 α . A second form of p38 β termed p38 β 2 is also known and of the two this is believed to be the major form. p38 α and p38 β 2 are expressed in many different tissues. However, in monocytes and macrophages p38 α is the predominant kinase activity [Lee, J.C., *ibid*; Jing, Y. *et al.*, 10 *J. Biol. Chem.*, 1996, 271, 10531-34; Hale, K.K. *et al.*, *J. Immun.*, 1999, 162, 4246-52]. p38 γ and p38 δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have ~63% and ~61% homology to p38 α respectively. p38 γ is predominantly expressed in skeletal muscle whilst p38 δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.
- 15 All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y.N. *et al.*, *FEBS Lett.*, 1995, 364, 7095-8012]. This dual
- 20 phosphorylation is effected by MKK6 and, under certain conditions, the related enzyme MKK3 [Enslen, H. *et al.*, *J. Biol. Chem.*, 1998, 273, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.
- 25 Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF- β -activated kinase) are some of the enzymes identified as upstream activators of MAPKKs. MEKK4/MTK1 is thought to be
- 30 activated by several GADD-45-like genes that are induced in response to

environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H., *Cell*, 1998, **95**, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor- β (TGF- β). TNF-stimulated activation of p38 is believed to be mediated by the recruitment of TRAF2 (TNF receptor
5 associated factor) and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and
10 stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and other substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice
15 engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1, IL-6, IFN- γ and IL-10 is also partially inhibited [Kotlyarov, A. *et al.*, *Nature Cell Biol.*, 1999, **1**, 94-7]. Further, MAPKAP K2 from embryonic stem cells from p38 α null mice was not activated in response to stress and these cells did not produce IL-6 in
20 response to IL-1 [Allen, M. *et al.*, *J. Exp. Med.*, 2000, **191**, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition, MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

25 Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μ M range [Lee, J.C. *et al.*, *Int. J. Immunopharm.*, 1988, **10**, 835] and exhibit activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J.C. *et al.*, *Annals N.Y. Acad. Sci.*, 1993, **696**, 149]. In addition, these small molecule inhibitors are
30 known to decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF)

and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA₂, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P., *Trends Cell Biol.*, 1997, 7, 353-61].

- 5 A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis,
- 10 bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to acquired immune deficiency syndrome (AIDS), cachexia secondary to
- 15 infection or malignancy, AIDS or AIDS related complex.

- Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic
- 20 inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition, IL-1 has been linked to diabetes and pancreatic β cells [Dinarello, C.A., *J. Clinical Immunology*, 1985, 5, 287-97].

- IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF and
- 25 LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis, which may contribute to increased adhesion of neutrophils to vascular
- 30 endothelial cells. Many diseases are characterised by massive neutrophil infiltration.

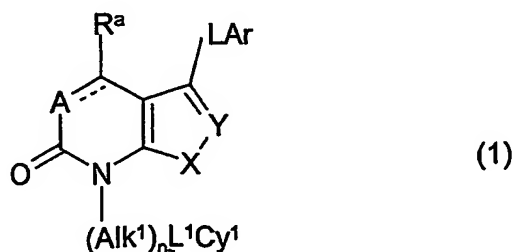
Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysosomal enzyme release and respiratory burst from neutrophils.

The central role of IL-1 and TNF together with other leukocyte-derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling, and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin), make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, 279, 1453-61; Griswold *et al.*, *Pharmacol. Commun.*, 1996, 7, 323-29].

We have now found a group of compounds which are potent and selective inhibitors of p38 kinase (p38 α , β , γ and δ) and the isoforms and splice variants thereof, especially p38 α , p38 β and p38 β 2. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described herein.

Thus, according to one aspect of the invention we provide a compound of formula (1):



25

wherein

the dashed line joining A and C(R^a) is present and represents a bond and A is a -N= atom or a -C(R^b)= group, or the dashed line is absent and A is a -N(R^b)- or -C(R^b)(R^c)- group;

- 5 R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C₁₋₆ alkyl, -CN, -CO₂H, -CO₂R¹ (where R¹ is an optionally substituted alkyl group), -CONH₂, -CONHR¹ or -CONR¹R² group (where R² is an optionally substituted alkyl group);

- 10 X is an -O-, -S- or substituted nitrogen atom or a -S(O)-, -S(O)₂- or -NH- group;

Y is a nitrogen or substituted carbon atom or a -CH= group;

n is zero or the integer 1;

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a covalent bond or a linker atom or group;

- 15 Cy¹ is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

- L is an atom or chain -(CH₂)_pHet(CH₂)_q- in which p and q, which may be the same or different, is each zero or the integer 1 and Het is an -O- or -S- atom or a
 20 -C(R^{3a})(R^{3b})- (where R^{3a} and R^{3b}, which may be the same or different, is each a hydrogen atom or an -OH or optionally substituted C₁₋₆ alkyl group), -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R^{3c})O- (where R^{3c} is a hydrogen atom or a straight or branched alkyl group), -N(R^{3c})NH-, -N(R^{3c})C(R^{3a})(R^{3b})-, -CON(R^{3c})-, -OC(O)N(R^{3c})-, -CSN(R^{3c})-, -N(R^{3c})CO-, -N(R^{3c})C(O)O-, -N(R^{3c})CS-,
 25 -S(O)₂N(R^{3c})-, -N(R^{3c})S(O)₂-, -N(R^{3c})CON(R^{3d})- (where R^{3d} is as defined for R^{3c} and may be the same or different), -N(R^{3c})CSN(R^{3d})- or -N(R^{3c})S(O)₂N(R^{3d})- group and, when one or both of p and q is the integer 1, Het is additionally a -N(R^{3c})- group; and

Ar is an optionally substituted aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

The present invention also provides a compound of formula (1) as depicted above, or a salt, solvate, hydrate or *N*-oxide thereof, wherein L is other than $-N(R^{3c})C(R^{3a})(R^{3b})-$, and the remaining substituents are as defined above.

It will be appreciated that compounds of formula (1) may have one or more
5 chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for
10 example keto ($CH_2C=O$)-enol ($CH=CHOH$) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

As used in formula (1) the terms "substituted nitrogen atom" and "substituted carbon atom" are intended to include groups such as those in which X is $-N(R^{10})-$ and
15 Y is $-C(R^{10})=$ where R^{10} is a substituent other than a hydrogen atom as generally or particularly defined hereinafter.

The following general terms as used herein in relation to compounds of the invention and intermediates thereto have the stated meaning below unless specifically defined otherwise.

20 Thus, as used herein, the term "alkyl" whether present as a group or part of a group includes straight or branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl or *tert*-butyl groups. Similarly, the terms "alkenyl" and "alkynyl" are intended to mean straight or branched C_{2-6} alkenyl or C_{2-6} alkynyl groups such as C_{2-4} alkenyl or C_{2-4} alkynyl
25 groups. Optional substituents which may be present on these groups include those optional substituents mentioned hereinafter in relation to Alk^1 when Alk^1 is an optionally substituted aliphatic chain.

The term halogen is intended to include fluorine, chlorine, bromine and iodine atoms.

30 The term "haloalkyl" is intended to include those alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular

examples of such groups include $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CHF}_2$, $-\text{CHCl}_2$, $-\text{CH}_2\text{F}$ and $-\text{CH}_2\text{Cl}$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-6} alkoxy, e.g. C_{1-4} alkoxy such as methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy and *tert*-butoxy. "Haloalkoxy" as used herein includes any of these alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-\text{OCF}_3$, $-\text{OCCl}_3$, $-\text{OCHF}_2$, $-\text{OCHCl}_2$, $-\text{OCH}_2\text{F}$ and $-\text{OCH}_2\text{Cl}$ groups.

As used herein, the term "alkylthio" is intended to include straight or branched C_{1-6} alkylthio, e.g. C_{1-4} alkylthio such as methylthio or ethylthio.

As used herein, the terms "alkylamino" or "dialkylamino" are intended to include the groups $-\text{NH}(\text{R}^{1a})$ and $-\text{N}(\text{R}^{1a})(\text{R}^{1b})$ where R^{1a} and R^{1b} is each independently an optionally substituted straight or branched alkyl group or both together with the N atom to which they are attached form an optionally substituted heterocycloalkyl group which may contain a further heteroatom or heteroatom-containing group such as an -O- or -S- atom or a $-\text{N}(\text{R}^{1a})$ - group. Particular examples of such optionally substituted heterocycloalkyl groups include optionally substituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and *N'*-(C_{1-6} alkyl)piperazinyl groups. The optional substituents which may be present on such heterocycloalkyl groups include those optional substituents as described hereinafter in relation to aliphatic chains such as Alk^1 .

When Alk^1 is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene, C_{2-6} alkenylene and C_{2-6} alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}_2-$, $-(\text{CH}_2)_3\text{CH}_2-$, $-\text{CH}(\text{CH}_3)(\text{CH}_2)_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_4\text{CH}_2-$, $-(\text{CH}_2)_5\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CHCH}_2-$, $-\text{CH}_2\text{CH}=\text{CH}-$, $-\text{CH}=\text{CHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$,

$-(\text{CH}_2)_2\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}\equiv\text{CCH}_2-$, $-\text{CH}_2\text{C}\equiv\text{C}-$, $-\text{C}\equiv\text{CCH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}\equiv\text{CCH}_2-$ and $-(\text{CH}_2)_2\text{C}\equiv\text{C}-$ chains.

Heteroaliphatic chains represented by Alk^1 in the compounds of formula (1) include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^2 where L^2 is a linker atom or group. Each L^2 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-\text{L}^2\text{CH}_2-$, $-\text{CH}_2\text{L}^2-$, $-\text{L}^2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{L}^2-$, $-\text{CH}_2\text{L}^2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{L}^2-$, $-\text{CH}_2\text{CH}_2\text{L}^2-$, $-\text{CH}_2\text{L}^2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{L}^2\text{CH}_2\text{CH}_2\text{L}^2-$, $-(\text{CH}_2)_2\text{L}^2\text{CH}_2-$, $-(\text{CH}_2)_3\text{L}^2\text{CH}_2-$, $-\text{L}^2(\text{CH}_2)_2\text{CH}_2-$, $-\text{L}^2\text{CH}_2\text{CH}=\text{CH}-$, $-\text{CH}=\text{CHCH}_2\text{L}^2-$ and $-(\text{CH}_2)_2\text{L}^2\text{CH}_2\text{CH}_2-$ chains.

When L^2 is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include $-\text{O}-$ or $-\text{S}-$ atoms and $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^3)-$ (where R^3 is a hydrogen atom or a straight or branched alkyl group), $-\text{N}(\text{R}^3)\text{O}-$, $-\text{N}(\text{R}^3)\text{NH}-$, $-\text{CON}(\text{R}^3)-$, $-\text{OC}(\text{O})\text{N}(\text{R}^3)-$, $-\text{CSN}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{CO}-$, $-\text{N}(\text{R}^3)\text{C}(\text{O})\text{O}-$, $-\text{N}(\text{R}^3)\text{CS}-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^3)\text{CON}(\text{R}^3)-$, $-\text{N}(\text{R}^3)\text{CSN}(\text{R}^3)-$ or $-\text{N}(\text{R}^3)\text{SO}_2\text{N}(\text{R}^3)-$ groups. Where L^2 contains two R^3 groups these may be the same or different.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, $-\text{OH}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^4$ (where R^4 is an optionally substituted straight or branched C_{1-6} alkyl group), e.g. $-\text{CO}_2\text{CH}_3$ or $-\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{CONHR}^4$, e.g. $-\text{CONHCH}_3$, $-\text{CON}(\text{R}^4)_2$, e.g. $-\text{CON}(\text{CH}_3)_2$, $-\text{COR}^4$, e.g. $-\text{COCH}_3$, C_{1-6} alkoxy, e.g. methoxy or ethoxy, halo(C_{1-6})alkoxy, e.g. trifluoromethoxy or difluoromethoxy, thiol ($-\text{SH}$), $-\text{S}(\text{O})\text{R}^4$, e.g. $-\text{S}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{R}^4$, e.g. $-\text{S}(\text{O})_2\text{CH}_3$, C_{1-6} alkylthio, e.g. methylthio or ethylthio, amino, $-\text{NHR}^4$, e.g. $-\text{NHCH}_3$, and $-\text{N}(\text{R}^4)_2$, e.g. $-\text{N}(\text{CH}_3)_2$, groups. Where two R^4 groups are present in any of the above substituents these may be the same or different.

In addition, when two R⁴ alkyl groups are present in any of the optional substituents just described these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom-containing group
5 selected from -O-, -S-, -N(R⁴)-, -C(O)- or -C(S)- groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When L¹ is present in compounds of formula (1) as a linker atom or group it may be any such atom or group as hereinbefore described in relation to L² linker
10 atoms and groups.

Optionally substituted cycloaliphatic groups represented by the group Cy¹ in compounds of the invention include optionally substituted C₃₋₁₀ cycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀ cycloalkyl, e.g. C₃₋₇ cycloalkyl, and C₃₋₁₀ cycloalkenyl, e.g. C₃₋₇ cycloalkenyl, groups.

Optionally substituted heterocycloaliphatic groups represented by the group
15 Cy¹ include optionally substituted C₃₋₁₀ heterocycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀ heterocycloalkyl, e.g. C₃₋₇ heterocycloalkyl, and C₃₋₁₀ heterocycloalkenyl, e.g. C₃₋₇ heterocycloalkenyl, groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-
20 containing groups L⁴ in place of or in addition to the ring carbon atoms where L⁴ is an atom or group as previously defined for L².

Optionally substituted polycycloaliphatic groups represented by the group Cy¹ include optionally substituted C₇₋₁₀ bi- or tricycloalkyl and C₇₋₁₀ bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups
25 represented by the group Cy¹ include optionally substituted C₇₋₁₀ bi- or tricycloalkyl and C₇₋₁₀ bi- or tricycloalkenyl groups containing one, two, three, four or more L⁴ atoms or groups in place of or in addition to the ring carbon atoms.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group
30 Cy¹ include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobut-2-en-1-yl, cyclopent-2-en-1-yl, cyclopent-3-en-1-yl, adamantyl,

- norbornyl, norbornenyl, dihydrofuryl, tetrahydrofuryl, tetrahydropyranyl, dihydrothienyl, tetrahydrothienyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, oxazolidinyl, oxazolidinonyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. imidazolin-2-yl, imidazolidinyl, pyrazolinyl, e.g. pyrazolin-2-yl, 5 pyrazolidinyl, 5,6-dihydro-2(1*H*)-pyrazinonyl, tetrahydropyrimidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminy, piperidinonyl, 1,4-dioxanyl, morpholinyl, morpholinonyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2*H*-1,3-, 6*H*-1,3-, 6*H*-1,2-, 2*H*-1,2- or 4*H*-1,4-oxazinyl, 1,2,5- 10 oxathiazinyl, isoxazinyl, e.g. *o*- or *p*-isoxazinyl, oxathiazinyl, e.g. 1,2,5- or 1,2,6- oxathiazinyl, 1,3,5-oxadiazinyl, dihydroisothiazolyl, dihydroisothiazole 1,1-dioxide, e.g. 2,3-dihydroisothiazole 1,1-dioxide, dihydropyrazinyl and tetrahydropyrazinyl groups.

- The optional substituents which may be present on the cycloaliphatic, 15 polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group Cy¹ include one, two, three or more substituents selected from halogen atoms, and C₁₋₆ alkyl, e.g. methyl or ethyl, halo(C₁₋₆)alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxy, e.g. -C(OH)(CF₃)₂, C₁₋₆ alkoxy, e.g. methoxy or ethoxy, halo(C₁₋₆)alkoxy, 20 e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C₁₋₆ alkylthio, e.g. methylthio or ethylthio, carbonyl (=O), thiocarbonyl (=S), imino (=NR^{4a}) (where R^{4a} is an -OH group or a C₁₋₆ alkyl group) or -(Alk³)_vR⁵ groups, in which Alk³ is a straight or branched C₁₋₃ alkylene chain, v is zero or the integer 1, and R⁵ is a C₃₋₈ cycloalkyl, -OH, -SH, -N(R⁶)(R⁷) (in which R⁶ and R⁷ is each 25 independently selected from a hydrogen atom and an optionally substituted alkyl or C₃₋₈ cycloalkyl group), -OR⁶, -SR⁶, -CN, -NO₂, -CO₂R⁶, -SOR⁶, -SO₂R⁶, -SO₃R⁶, -OCO₂R⁶, -C(O)R⁶, -OC(O)R⁶, -C(S)R⁶, -C(O)N(R⁶)(R⁷), -OC(O)N(R⁶)(R⁷), -N(R⁶)C(O)R⁷, -C(S)N(R⁶)(R⁷), -N(R⁶)C(S)R⁷, -SO₂N(R⁶)(R⁷), -N(R⁶)SO₂R⁷, -N(R⁶)C(O)N(R⁷)(R⁸) (where R⁸ is as defined for R⁶), -N(R⁶)C(S)N(R⁷)(R⁸) or 30 -N(R⁶)SO₂N(R⁷)(R⁸) group, or an optionally substituted aromatic or heteroaromatic group.

Particular examples of Alk^3 chains include $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}(\text{CH}_3)\text{CH}_2-$ chains.

When R^5 , R^6 , R^7 and/or R^8 is present as a C_{3-8} cycloalkyl group it may be, for example, a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. Optional
 5 substituents which may be present on such groups include, for example, one, two or three substituents, which may be the same or different, selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, and hydroxy or C_{1-6} alkoxy groups, e.g. methoxy, ethoxy or isopropoxy groups.

When the groups R^6 and R^7 or R^7 and R^8 are both alkyl groups these groups
 10 may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom or heteroatom-containing group selected from $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^7)-$, $-\text{C}(\text{O})-$ and $-\text{C}(\text{S})-$ groups. Particular examples of such heterocyclic rings include piperidinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl,
 15 imidazolidinyl and piperazinyl rings.

When R^5 is an optionally substituted aromatic or heteroaromatic group it may be any such group as described hereinafter in relation to Cy^1 .

Additionally, when the group Cy^1 is a heterocycloaliphatic or heteropolycycloaliphatic group containing one or more nitrogen atoms each nitrogen
 20 atom may be optionally substituted by a group $-(\text{L}^5)_p(\text{Alk}^4)_q\text{R}^9$ in which L^5 is a $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})_2-$, $-\text{CON}(\text{R}^6)-$ or $-\text{SO}_2\text{N}(\text{R}^6)-$ group; p is zero or the integer 1; Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or the integer 1; and R^9 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic,
 25 aromatic or heteroaromatic group as herein described in relation to Cy^1 .

When Alk^4 is present as an aliphatic or heteroaliphatic chain it may be, for example, any aliphatic or heteroaliphatic chain as hereinbefore described for Alk^1 .

Optionally substituted aromatic groups represented by the group Cy^1 include, for example, monocyclic and bicyclic fused ring C_{6-12} aromatic groups, such as
 30 phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Heteroaromatic groups represented by the group Cy¹ include, for example, C₁₋₉ heteroaromatic groups containing, for example, one, two, three or four heteroatoms selected from oxygen, sulphur and nitrogen atoms. In general, the heteroaromatic groups may be, for example, monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include, for example, five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur and nitrogen atoms. Bicyclic heteroaromatic groups include, for example, eight- to thirteen-membered fused ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur and nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, *N*-(C₁₋₆ alkyl)imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, (2,3-dihydro)benzofuryl, benzothienyl, (2,3-dihydro)benzothienyl, benzotriazolyl, indolyl, indolinyl, indazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, (3,4-dihydro)-benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, imidazo[1,5-*a*]pyridinyl, imidazo[1,5-*a*]pyrazinyl, imidazo[1,5-*c*]pyrimidinyl, pyrido[3,4-*b*]pyridinyl, pyrido[3,2-*b*]pyridinyl, pyrido[4,3-*b*]pyridinyl, quinolinyl, isoquinolinyl, phthalazinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, imidyl, e.g. succinimidyl, phthalimidyl or naphthalimidyl such as 1,8-naphthalimidyl, pyrazolo[4,3-*d*]pyrimidinyl, furo[3,2-*d*]pyrimidinyl, thieno[3,2-*d*]pyrimidinyl, pyrrolo[3,2-*d*]pyrimidinyl, pyrazolo[3,2-*b*]pyridinyl, furo[3,2-*b*]pyridinyl, thieno[3,2-*b*]pyridinyl, pyrrolo[3,2-*b*]pyridinyl, thiazolo[3,2-*a*]pyridinyl, pyrido[1,2-*a*]pyrimidinyl, tetrahydroimidazo[1,2-*a*]pyrimidinyl and dihydroimidazo[1,2-*a*]pyrimidinyl groups.

Optional substituents which may be present on aromatic or heteroaromatic groups represented by the group Cy¹ include one, two, three or more substituents, each selected from an atom or group R¹⁰ in which R¹⁰ is R^{10a} or -L⁶Alk⁵(R^{10a})_n, where

- R^{10a} is a halogen atom, or an amino ($-\text{NH}_2$), substituted amino, nitro, cyano, hydroxy ($-\text{OH}$), substituted hydroxy, formyl, carboxy ($-\text{CO}_2\text{H}$), esterified carboxy, thiol ($-\text{SH}$), substituted thiol, $-\text{COR}^{11}$ (where R^{11} is an $-\text{L}^6\text{Alk}^3(\text{R}^{10a})_r$, aryl or heteroaryl group), $-\text{CSR}^{11}$, $-\text{SO}_3\text{H}$, $-\text{SOR}^{11}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_3\text{R}^{11}$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHR}^{11}$,
 5 $-\text{SO}_2\text{N}(\text{R}^{11})_2$, $-\text{CONH}_2$, $-\text{CSNH}_2$, $-\text{CONHR}^{11}$, $-\text{CSNHR}^{11}$, $-\text{CON}(\text{R}^{11})_2$, $-\text{CSN}(\text{R}^{11})_2$, $-\text{N}(\text{R}^{12})\text{SO}_2\text{R}^{11}$ (where R^{12} is a hydrogen atom or a straight or branched alkyl group), $-\text{N}(\text{SO}_2\text{R}^{11})_2$, $-\text{N}(\text{R}^{12})\text{SO}_2\text{NH}_2$, $-\text{N}(\text{R}^{12})\text{SO}_2\text{NHR}^{11}$, $-\text{N}(\text{R}^{12})\text{SO}_2\text{N}(\text{R}^{11})_2$, $-\text{N}(\text{R}^{12})\text{COR}^{11}$, $-\text{N}(\text{R}^{12})\text{CONH}_2$, $-\text{N}(\text{R}^{12})\text{CONHR}^{11}$, $-\text{N}(\text{R}^{12})\text{CON}(\text{R}^{11})_2$, $-\text{N}(\text{R}^{12})\text{CSNH}_2$, $-\text{N}(\text{R}^{12})\text{CSNHR}^{11}$, $-\text{N}(\text{R}^{12})\text{CSN}(\text{R}^{11})_2$, $-\text{N}(\text{R}^{12})\text{CSR}^{11}$,
 10 $-\text{N}(\text{R}^{12})\text{C}(\text{O})\text{OR}^{11}$, $-\text{SO}_2\text{NHet}^1$ (where $-\text{NHet}^1$ is an optionally substituted C_{5-7} cyclic amino group optionally containing one or more other $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^{12})-$, $-\text{C}(\text{O})-$ or $-\text{C}(\text{S})-$ groups), $-\text{CONHet}^1$, $-\text{CSNHet}^1$, $-\text{N}(\text{R}^{12})\text{SO}_2\text{NHet}^1$, $-\text{N}(\text{R}^{12})\text{CONHet}^1$, $-\text{N}(\text{R}^{12})\text{CSNHet}^1$, $-\text{SO}_2\text{N}(\text{R}^{12})\text{Het}^2$ (where $-\text{Het}^2$ is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more
 15 other $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^{12})-$, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$ groups), $-\text{Het}^2$, $-\text{CON}(\text{R}^{12})\text{Het}^2$, $-\text{CSN}(\text{R}^{12})\text{Het}^2$, $-\text{N}(\text{R}^{12})\text{CON}(\text{R}^{12})\text{Het}^2$, $-\text{N}(\text{R}^{12})\text{CSN}(\text{R}^{12})\text{Het}^2$, $-\text{N}(\text{R}^{12})\text{SO}_2\text{N}(\text{R}^{12})\text{Het}^2$, aryl or heteroaryl group; L^6 is a covalent bond or a linker atom or group as hereinbefore defined for L^2 ; Alk^5 is an optionally substituted straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain,
 20 optionally interrupted by one, two or three $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$ or $-\text{N}(\text{R}^{12})-$, e.g. $-\text{N}(\text{CH}_3)-$, groups; and r is zero or the integer 1, 2, or 3. It will be appreciated that when two R^{11} or R^{12} groups are present in one of the above substituents the R^{11} and R^{12} groups may be the same or different.

- When in the group $-\text{L}^6\text{Alk}^5(\text{R}^{10a})_r$, r is an integer 1, 2 or 3, it is to be understood
 25 that the substituent or substituents R^{10a} may be present on any suitable carbon atom in Alk^5 . Where more than one R^{10a} substituent is present these may be the same or different and may be present on the same atom or on different atoms in Alk^5 . Clearly, when r is zero and no substituent R^{10a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^5 becomes an alkyl, alkenyl or alkynyl group.

When R^{10a} is a substituted amino group it may be, for example, a group $-NHR^{11}$ (where R^{11} is as defined above) or a group $-N(R^{11})_2$ wherein each R^{11} group is the same or different.

When R^{10a} is a halogen atom it may be, for example, a fluorine, chlorine,
5 bromine or iodine atom.

When R^{10a} is a substituted hydroxy or substituted thiol group it may be, for example, a group $-OR^{11}$ or $-SR^{12}$ respectively.

Esterified carboxy groups represented by the group R^{10a} include groups of formula $-CO_2Alk^6$ wherein Alk^6 is a straight or branched, optionally substituted C_{1-8}
10 alkyl group such as a methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl or *tert*-butyl group; a C_{6-12} aryl(C_{1-8} alkyl) group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy(C_{1-8} alkyl) group such as an optionally substituted phenoxymethyl,
15 phenoxyethyl, 1-naphthyloxymethyl or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy(C_{1-8} alkyl) group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aryloxy(C_{1-8} alkyl) group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^6 group include R^{10a} atoms and groups as described above.

When Alk^5 is present in or as a substituent it may be, for example, a $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-C(CH_3)_2CH_2-$, $-CH=CH-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH_2CH=CH-$, $-C\equiv C-$, $-C\equiv CCH_2-$, $-CH_2C\equiv C-$, $-C\equiv CCH_2CH_2-$, $-CH_2C\equiv CCH_2-$ or $-CH_2CH_2C\equiv C-$ chain,
25 optionally interrupted by one, two or three -O- or -S- atoms or -S(O)-, -S(O)₂- or -N(R^{12})-, e.g. -N(CH₃)-, groups. The aliphatic chains represented by Alk^5 may be optionally substituted by one, two or three halogen atoms in addition to any R^{10a} groups that may be present.

Aryl or heteroaryl groups represented by the groups R^{10a} or R^{11} include mono-
30 and bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Cy^1 . The aromatic and heteroaromatic groups may be

attached to the group Cy¹ in compounds of formula (1) by any carbon atom or heteroatom, e.g. nitrogen atom, as appropriate.

It will be appreciated that when -NHet¹ or -Het² forms part of a substituent R¹⁰ the heteroatoms or heteroatom-containing groups that may be present within the ring

5 -NHet¹ or -Het² take the place of carbon atoms within the parent carbocyclic ring.

Thus, when -NHet¹ or -Het² forms part of a substituent R¹⁰ each may be, for example, an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group.

10 Additionally, -Het² may represent, for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ include those substituents described above when Cy¹ is a heterocycloaliphatic group.

Particularly useful atoms or groups represented by R¹⁰ include fluorine, chlorine, bromine or iodine atoms, and C₁₋₆ alkyl, e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or *tert*-butyl, optionally substituted phenyl, pyridinyl, pyrimidinyl, pyrrolyl, furyl,

15 thiazolyl or thienyl, C₁₋₆ hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxy-(C₁₋₆ alkyl), e.g. carboxyethyl, C₁₋₆ alkylthio, e.g. methylthio or ethylthio, carboxy(C₁₋₆ alkyl)thio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆ alkoxy, e.g. methoxy or ethoxy, hydroxy(C₁₋₆ alkoxy), e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridinyloxy, thiazolyloxy, phenylthio or pyridinylthio, C₃₋₇

20 cycloalkyl, e.g. cyclobutyl or cyclopentyl, C₅₋₇ cycloalkoxy, e.g. cyclopentyloxy, halo(C₁₋₆ alkyl), e.g. trifluoromethyl, halo(C₁₋₆ alkoxy), e.g. trifluoromethoxy, C₁₋₆ alkylamino, e.g. methylamino, ethylamino, -CH(CH₃)NH₂ or -C(CH₃)₂NH₂, halo(C₁₋₆ alkyl)amino, e.g. fluoro(C₁₋₆ alkyl)amino such as -CH(CF₃)NH₂ or -C(CF₃)₂NH₂, amino (-NH₂), amino(C₁₋₆ alkyl), e.g. aminomethyl or aminoethyl, di(C₁₋₆ alkyl)amino, e.g.

25 dimethylamino or diethylamino, C₁₋₆ alkylamino(C₁₋₆ alkyl), e.g. ethylaminoethyl, di-(C₁₋₆ alkyl)amino(C₁₋₆ alkyl), e.g. diethylaminoethyl, amino(C₁₋₆ alkoxy), e.g. aminoethoxy, C₁₋₆ alkylamino(C₁₋₆ alkoxy), e.g. methylaminoethoxy, di(C₁₋₆ alkyl)amino(C₁₋₆ alkoxy), e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy or dimethylaminopropoxy, imido, such as phthalimido or

30 naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, hydroxy (-OH), formyl [HC(O)-], carboxy (-CO₂H), -CO₂Alk⁶ (where Alk⁶ is as defined above), C₁₋₆ alkanoyl, e.g. acetyl,

- optionally substituted benzoyl, thiol (-SH), thio(C₁₋₆ alkyl), e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆ alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆ alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, di(C₁₋₆ alkyl)aminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆ alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, di(C₁₋₆ alkyl)aminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, amino(C₁₋₆ alkyl)aminocarbonyl, e.g. aminoethylaminocarbonyl, di(C₁₋₆ alkyl)amino(C₁₋₆ alkyl)aminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆ alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, di(C₁₋₆ alkyl)aminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆ alkylaminocarbonyl(C₁₋₆ alkyl)amino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C₁₋₆ alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, di(C₁₋₆ alkyl)aminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆ alkylaminothiocarbonyl(C₁₋₆ alkyl)amino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆ alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, di(C₁₋₆ alkyl)sulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NH-SO₂NH₂), C₁₋₆ alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, di(C₁₋₆ alkyl)aminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinylsulphonylamino or morpholinylsulphonyl(C₁₋₆ alkyl)amino, optionally substituted phenylaminosulphonylamino, C₁₋₆ alkanoylamino, e.g. acetylamino, amino(C₁₋₆ alkanoyl)amino, e.g. aminoacetylamino, di(C₁₋₆ alkyl)amino(C₁₋₆ alkanoyl)amino, e.g. dimethylaminoacetylamino, C₁₋₆ alkanoylamino(C₁₋₆ alkyl), e.g. acetylaminomethyl, C₁₋₆ alkanoylamino(C₁₋₆ alkyl)amino, e.g. acetamidoethylamino, C₁₋₆ alkoxy-carbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or *tert*-butoxycarbonylamino, or optionally substituted benzyloxy, pyridinylmethoxy,

thiazolymethoxy, benzyloxycarbonylamino, benzyloxycarbonylamino(C₁₋₆ alkyl), e.g. benzyloxycarbonylaminoethyl, benzothio, pyridinylmethylthio or thiazolymethylthio groups.

- A further particularly useful group of substituents represented by R¹⁰ when
- 5 present on aromatic or heteroaromatic groups includes substituents of formula -L⁶Alk⁵R^{10a} where L⁶ is preferably a covalent bond, an -O- or -S- atom or a -N(R³)-, -C(O)-, -C(O)O-, -OC(O)-, -N(R³)CO-, -CON(R³)- or -N(R³)S(O)₂- group; Alk⁵ is an optionally substituted C₁₋₆ alkylene group optionally interrupted by one or two -O- or -S- atoms or -N(R¹²)-, -C(O)-, -C(S)-, -CON(R¹²)- or -N(R¹²)CO- groups; and R^{10a} is an
- 10 optionally substituted -Het² group as herein defined or an optionally substituted heteroaromatic group as hereinbefore described in relation to Cy¹.

Where desired, two R¹⁰ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆ alkylenedioxy group such as methylenedioxy or ethylenedioxy.

- 15 It will be appreciated that where two or more R¹⁰ substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position on the aromatic or heteroaromatic group represented by the group Cy¹.

- The optionally substituted aromatic or heteroaromatic group represented by
- 20 Ar in compounds of the invention may be any aromatic or heteroaromatic group as hereinbefore described for Cy¹. Optional substituents which may be present include those R¹⁰ atoms and groups as generally or particularly described in relation to Cy¹ aromatic and heteroaromatic groups.

- In general, in compounds of formula (1) X is preferably an -O- or -S- atom,
- 25 and is especially a -S- atom.

In another group of compounds of formula (1) R^a is preferably a hydrogen atom or a C₁₋₄ alkyl group, especially a methyl, ethyl, *n*-propyl or isopropyl group. In particular, R^a is a methyl group or more especially a hydrogen atom.

- In another particular class of compounds of formula (1) the bond represented
- 30 by the dashed line is present and A is a -C(R^b)= group. In these compounds R^b is preferably a hydrogen atom or a C₁₋₄ alkyl group, especially a methyl, ethyl, *n*-propyl

or isopropyl group. More particularly, R^b is a methyl group or more especially a hydrogen atom.

When in compounds of formula (1) n is the integer 1, Alk^1 is preferably an optionally substituted C_{1-6} alkylene chain, especially an optionally substituted $-CH_2-$,
 5 $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH(CH_3)-$ chain, more especially a $-CH_2-$ or $-CH_2CH_2-$ chain, and most especially a $-CH_2-$ chain.

In one class of compounds of formula (1) n is zero.

The group L^1 in compounds of formula (1) is preferably a covalent bond, an $-O-$ or $-S-$ atom or an $-N(R^3)-$, especially $-NH-$ or $-N(CH_3)-$, $-C(O)-$, $-C(S)-$, $-S(O)-$ or
 10 $-S(O)_2-$ group. More particularly, L^1 is a covalent bond, an $-O-$ or $-S-$ atom or a $-NH-$ group. L^1 is most preferably a covalent bond.

Cy^1 in compounds of formula (1) is preferably an optionally substituted cycloaliphatic, aromatic or heteroaromatic group as hereinbefore generally and particularly defined.

15 Particularly preferred Cy^1 optionally substituted cycloaliphatic groups include optionally substituted C_{3-7} cycloalkyl groups, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups.

Particularly preferred optional substituents which may be present on Cy^1 optionally substituted cycloaliphatic groups include halogen atoms, especially
 20 fluorine, chlorine or bromine atoms, C_{1-6} alkyl groups, especially C_{1-3} alkyl groups, most especially a methyl group, halo(C_{1-6} alkyl) groups, especially fluoro(C_{1-6} alkyl) groups, most especially a $-CF_3$ group, C_{1-6} alkoxy groups, especially a methoxy, ethoxy, propoxy or isopropoxy group, and halo(C_{1-6} alkoxy) groups, especially fluoro(C_{1-6} alkoxy) groups, most especially a $-OCF_3$ group, or a cyano ($-CN$),
 25 esterified carboxy, especially $-CO_2CH_3$ or $-CO_2C(CH_3)_3$, nitro ($-NO_2$), amino ($-NH_2$), substituted amino, especially $-NHCH_3$ or $-N(CH_3)_2$, $-C(O)R^6$, especially $-C(O)CH_3$, or $-N(R^6)C(O)R^7$, especially $-NHCOCH_3$, group.

Particularly preferred Cy^1 aromatic groups include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally
 30 substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four

heteroatoms selected from oxygen, sulphur and nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl and triazinyl groups.

- 5 Particularly preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include atoms or groups -R^{10a} and -L⁶Alk⁵(R^{10a})_r as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, C₁₋₆ alkyl groups, especially C₁₋₃ alkyl groups, most especially a methyl group, halo(C₁₋₆ alkyl) groups, especially
- 10 fluoro(C₁₋₆ alkyl) groups, most especially a -CF₃ group, C₁₋₆ alkoxy groups, especially a methoxy, ethoxy, *n*-propoxy or isopropoxy group, and halo(C₁₋₆ alkoxy) groups, especially fluoro(C₁₋₆ alkoxy) groups, most especially a -OCF₃ group, or a cyano (-CN), carboxy (-CO₂H), esterified carboxy (-CO₂Alk⁶), especially -CO₂CH₃, -CO₂CH₂CH₃ or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino,
- 15 especially -NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃, group.

- Further preferred optional substituents which may be present on Cy¹ aromatic or heteroaromatic groups include groups of formula -L⁶Alk⁵(R^{10a})_r in which r is the integer 1; L⁶ is a covalent bond, an -O- or -S- atom, or a -N(R³)-, especially -NH- or
- 20 -N(CH₃)-, -C(O)-, -C(S)-, -C(O)O-, -OC(O)-, -N(R³)CO-, especially -NHCO-, or -CON(R³)-, especially -CONH-, group; Alk⁵ is a C₁₋₆ alkylene chain, especially a -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- or -CH₂CH₂CH₂CH₂- chain; and R^{10a} is a substituted hydroxy group, especially a -OCH₃, -OCH₂CH₃ or -OCH(CH₃)₂ group, a substituted amino group, especially a -N(CH₃)₂ or -N(CH₂CH₃)₂ group, or a -Het²
- 25 group, especially an optionally substituted monocyclic C₅₋₇ carbocyclic group containing one, two or three -O-, -S-, -N(R¹²)-, especially -NH- or -N(CH₃)-, or -C(O)- groups within the ring structure as previously described, most especially an optionally substituted pyrrolidinyl, imidazolidinyl, piperidinyl, e.g. *N*-methylpiperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group, or R^{10a} is an
- 30 optionally substituted heteroaromatic group, especially a five- or six-membered monocyclic heteroaromatic group containing one, two, three or four heteroatoms

selected from oxygen, sulphur and nitrogen atoms, such as an optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, triazolyl, pyridinyl, pyrimidinyl, triazinyl, pyridazinyl or pyrazinyl group. Particularly preferred optional substituents on the -Het² groups just described include hydroxy (-OH) and carboxy (-CO₂H) groups or
 5 those preferred optional substituents just described in relation to the group Cy¹.

In one particularly preferred group of compounds of formula (1) Cy¹ is an optionally substituted phenyl group, especially a phenyl group optionally substituted by one, two or three optional substituents where at least one, and preferably two, optional substituents are located *ortho* to the bond joining Cy¹ to the remainder of the
 10 compound of formula (1). Particularly preferred *ortho* substituents include halogen atoms, especially fluorine or chlorine atoms, C₁₋₃ alkyl groups, especially methyl, C₁₋₃ alkoxy groups, especially methoxy, halo(C₁₋₃ alkyl) groups, especially -CF₃, halo(C₁₋₃ alkoxy) groups, especially -OCF₃, and cyano (-CN) groups. In this class of compounds a second or third optional substituent when present in a position other
 15 than the *ortho* positions of the ring Cy¹ may be preferably an atom or group -R^{10a} or -L⁶Alk⁵(R^{10a})_r as herein generally and particularly described.

In one specific embodiment, Cy¹ is phenyl. In another specific embodiment, Cy¹ is cyclopropyl.

The group Y in compounds of formula (1) is preferably a -CH= group or a
 20 substituted carbon atom. Particular substituted carbon atoms include those where Y is -C(R¹⁰)= wherein R¹⁰ is as generally or particularly described above, especially those -R^{10a} and -L⁶Alk⁵(R^{10a})_r substituents just described with respect to those preferred optional substituents present on Cy¹ aromatic or heteroaromatic groups. Particularly useful compounds of formula (1) are those compounds wherein Y is
 25 -CH= or -C(R¹⁰)= in which R¹⁰ is a -CN, -CONH₂, -CONHR¹¹, -CON(R¹¹)₂, -CONHet¹, -CON(R¹²)Het², -CON(R¹²)Alk⁵Het², or esterified carboxy, particularly -CO₂Alk⁶, group as generally or particularly described herein. Especially favoured compounds of formula (1) are those compounds wherein Y is -C(R¹⁰)= in which R¹⁰ is -CN, -CONH₂ or -CO₂Alk⁶ and Alk⁶ is C₁₋₄ alkyl (especially ethyl).

30 LAr in compounds of the invention may typically be -OAr, -SAr, -C(R^{3a})(R^{3b})Ar [especially -CH₂Ar or -CH(OH)Ar], -C(R^{3a})(R^{3b})CH₂Ar (especially

- CH₂CH₂Ar), -N(R^{3c})NHAr (especially -NHNHAr), -N(R^{3c})CH₂Ar [especially -NHCH₂Ar or -N(CH₃)CH₂Ar], -N(R^{3c})C(R^{3a})(R^{3b})Ar [especially -NHCH(CH₃)Ar], -N(R^{3c})COAr (especially -NHCOAr), -S(O)₂N(R^{3c})Ar (especially -SO₂NHAr), -N(R^{3c})S(O)₂Ar (especially -NHSO₂Ar) or -N(R^{3c})CON(R^{3d})Ar (especially -NHCONHAr).

LAr in compounds of the invention may in particular be an -OAr, -SAr, -C(R^{3a})(R^{3b})Ar, especially -CH₂Ar, or -N(R^{3c})CH₂Ar, especially -NHCH₂Ar, group.

- Particularly preferred Ar aromatic groups in compounds of formula (1) include optionally substituted phenyl groups. Particularly preferred heteroaromatic groups include optionally substituted monocyclic heteroaromatic groups, especially optionally substituted five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur and nitrogen atoms. Particularly preferred optionally substituted monocyclic heteroaromatic groups include optionally substituted furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl or triazinyl groups.

- Particularly preferred optional substituents which may be present on Ar aromatic or heteroaromatic groups include atoms or groups -R^{10a} or -L⁶Alk⁵(R^{10a})_r as hereinbefore defined. Particularly useful optional substituents include halogen atoms, especially fluorine, chlorine or bromine atoms, C₁₋₆ alkyl groups, especially C₁₋₃ alkyl groups, most especially a methyl group, halo(C₁₋₆ alkyl) groups, especially fluoro(C₁₋₆ alkyl) groups, most especially a -CF₃ group, C₁₋₆ alkoxy groups, especially a methoxy, ethoxy, *n*-propoxy or isopropoxy group, and halo(C₁₋₆ alkoxy) groups, especially fluoro(C₁₋₆ alkoxy) groups, most especially a -OCF₃ group, or a cyano (-CN), esterified carboxy, especially -CO₂CH₃ or -CO₂C(CH₃)₃, nitro (-NO₂), amino (-NH₂), substituted amino, especially -NHCH₃ or -N(CH₃)₂, -COR¹¹, especially -COCH₃, or -N(R¹²)COR¹¹, especially -NHCOCH₃, group.

- Particularly useful Ar groups in compounds of formula (1) include phenyl and mono- or disubstituted phenyl groups in which each substituent is in particular a -R^{10a} or -L⁶Alk⁵(R^{10a})_r atom or group as just defined and is especially a halogen atom or a C₁₋₃ alkyl, C₁₋₃ alkoxy or -CN group.

Specific Ar groups in the compounds of formula (1) above include phenyl, halophenyl (especially chlorophenyl; in particular 4-chlorophenyl), dihalophenyl (especially difluorophenyl; in particular 2,6-difluorophenyl), (C₁₋₆ alkyl)phenyl (especially methylphenyl; in particular 3-methylphenyl or 4-methylphenyl), pyridinyl
5 (in particular pyridin-2-yl) and (C₁₋₆ alkyl)pyridinyl (especially methylpyridinyl; in particular 6-methylpyridin-2-yl).

Particularly useful compounds of the invention include each of the compounds described in the Examples hereinafter, and the salts, solvates, hydrates and *N*-oxides thereof.

10 Compounds according to the invention are potent and selective inhibitors of p38 kinases, including all isoforms and splice variants thereof. More specifically, the compounds of the invention are inhibitors of p38 α , p38 β and p38 β 2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

15 The compounds of formula (1) are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Furthermore, the invention
20 extends to the administration to a human of an effective amount of a p38 inhibitor for treating any such disease or disorder.

The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by excessive or unregulated pro-inflammatory cytokine production, including for example excessive
25 or unregulated TNF, IL-1, IL-6 and IL-8 production in a human or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Furthermore, the invention extends to the administration to a human of an effective amount of a p38 inhibitor for treating any such disease or disorder.

30 Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8

include without limitation autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs host disease and psoriasis.

The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome, and acute or chronic pancreatitis.

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma and multiple myeloma.

Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias and neurodegenerative disease caused by traumatic injury.

Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

In addition, p38 inhibitors of this invention exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2, otherwise known as cyclooxygenase-2 (COX-2), and are therefore of use in therapy. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular, these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly, additional p38-mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

TNF-mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, reperfusion injury, graft vs host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, and viral infections such as HIV, CMV, influenza and herpes; veterinary viral infections such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; and retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus and canine immunodeficiency virus.

Compounds of the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to

upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the TNF-inhibiting compounds of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3,
5 Cytomegalovirus (CMV), influenza, adenovirus and the herpes group of viruses such as *Herpes zoster* and *Herpes simplex*.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock syndrome,
10 inflammatory reaction induced by endotoxin, diabetes, pancreatic β -cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis, inflammatory
15 bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The increased IL-8 production associated with each of these diseases is responsible for the chemotaxis of neutrophils into inflammatory sites. This is due to the unique property of IL-8 (in comparison to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and
20 activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in neutrophil infiltration.

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al.*, *Clin. Infec.*
25 *Dis.*, 1997, 26, 840; Grunberg *et al.*, *Am. J. Crit. Care Med.*, 1997, 155, 1362; Zhu *et al.*, *J. Clin. Invest.*, 1996, 97, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al.*, *J. Clin. Invest.*, 1995, 96, 549]. Therefore, p38 inhibitors of the invention may be used for
30 the treatment or prophylaxis of the common cold or respiratory viral infection caused

by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus or adenovirus.

For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine mediated disease the compounds according to the invention may be administered to a human or mammal as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (1) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for

injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain
5 agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

10 For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

15 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds according to the present invention
20 may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated
25 in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds according to the present
30 invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal

or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

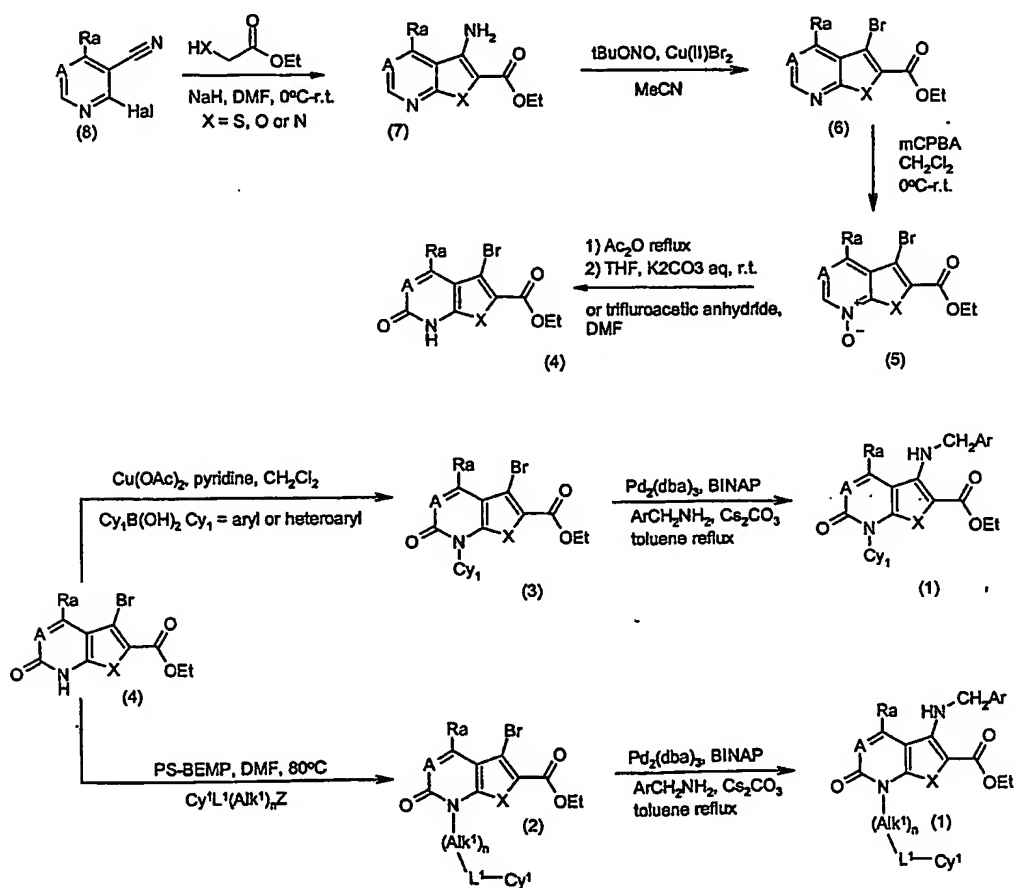
For rectal administration the compounds according to the present invention
5 may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

10 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight for oral or buccal administration,
15 from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In
20 the following process description, the symbols Ar, Cy¹, Alk¹, n, L¹, L, R^a, R^b, R^c, A, X and Y when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the
25 final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, John Wiley and Sons, 3rd edition, 1999]. In some instances, deprotection may be the
30 final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus, according to a further aspect of the invention a compound of formula (1) in which A is a $-C(R^b)=$ group, X is an -O- or -S- atom or a -NH- group, Y is a substituted carbon atom in which the substituent is an esterified carboxy group, for example a $-CO_2Alk^6$ group, and L is a $-NHCH_2-$ chain may be prepared according to the reactions set out in Scheme 1 below. In the Scheme the preparation of an ethyl ester is specifically shown, but it will be appreciated that other esters may be obtained by simply varying the ester starting material and if appropriate any reaction conditions:

10 Scheme 1



Thus, in Scheme 1 a compound of formula (1) may be prepared by reaction of a compound of formula (2) or (3) with an amine ArCH_2NH_2 in the presence of a palladium catalyst. The reaction may be conveniently carried out in a solvent such as toluene at an elevated temperature, e.g. the reflux temperature, using a catalyst such as tris(dibenzylideneacetone)dipalladium(0), a phosphine ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and a base such as caesium carbonate. Where desired, alternative reaction conditions may be used, for example as described in the literature [Luker *et al.*, *Tetrahedron Lett.*, 2001, 41, 7731; Buchwald, S.L., *J. Org. Chem.*, 2000, 65, 1144; Hartwig, J.F., *Angew. Chem. Int. Ed. Engl.*, 1998, 37, 2046].

Intermediates of formula (2) may be prepared by reaction of a compound of formula (4) with an alkylating agent of formula $\text{Cy}^1\text{L}^1(\text{Alk}^1)_n\text{Z}$, where Z is a leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom, or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy, or arylsulphonyloxy, e.g. phenylsulphonyloxy, group.

The reaction may be performed in the presence of a solvent, for example a substituted amide such as *N,N*-dimethylformamide, optionally in the presence of a base, for example an inorganic base such as sodium hydride, or an organic base such as an organic amine, e.g. a cyclic amine such as 1,5-diazabicyclo[4.3.0]non-5-ene, or a resin-bound organic amine such as resin-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP), at an elevated temperature, for example 60 to 100°C.

Intermediates of formula (3) may be prepared by the reaction of a compound of formula (4) with a boronic acid of formula $\text{Cy}^1\text{B}(\text{OH})_2$ in which Cy^1 is an aryl or heteroaryl group. The reaction may be performed in an organic solvent, for example a halogenated hydrocarbon such as dichloromethane or dichloroethane, in the presence of a copper reagent, for example a copper(II) reagent such as copper(II) acetate, optionally in the presence of an oxidant, for example 2,2,6,6-tetramethyl-1-piperidinyloxy or pyridine *N*-oxide, optionally in the presence of a base, for example an organic amine such as an alkylamine, e.g. triethylamine, or an aromatic amine, e.g. pyridine, at a temperature from around ambient to the reflux temperature [see,

for example, Chan, D.T. *et al.*, *Tetrahedron Lett.*, 1998, 2933; Lam, P.Y.S. *et al.*, *Tetrahedron Lett.*, 2001, 3415].

It will be appreciated that if desired the reactions just described may be carried out in the reverse order so that the amination using ArCH_2NH_2 is performed first with the intermediate of formula (4) followed by alkylation/arylation to yield the compound of formula (1).

Intermediate pyridinones of formula (4) may be prepared from pyridine *N*-oxides of formula (5) by sequential reaction with an anhydride, for example acetic anhydride, at an elevated temperature, for example the reflux temperature, followed by reaction with an inorganic base, for example a carbonate such as aqueous potassium carbonate, in a solvent such as an ether, for example a cyclic ether, e.g. tetrahydrofuran, at around ambient temperature. Alternatively, the reaction may be performed using trifluoroacetic anhydride in *N,N*-dimethylformamide from 0°C to ambient temperature conditions [see, for example, Konno *et al.*, *Heterocycles*, 1986, 24, 2169].

Pyridine *N*-oxides of formula (5) may be formed by oxidation of pyridines of formula (6) using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C; or alternatively by reaction with a peracid such as peracetic acid or *m*-chloroperoxybenzoic acid in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, or an alcohol, e.g. *tert*-butanol, at a temperature from the ambient temperature to the reflux temperature.

Intermediate pyridines of formula (6) in Scheme 1 may be obtained by standard methods such as, for example, the Sandmeyer reaction. Thus, for example, a bromide of formula (6) may be prepared by treatment of an aryl amine of formula (7) with an alkyl nitrite, for example *tert*-butyl nitrite, and a copper salt, for example copper(II) bromide, in the presence of a solvent, for example a nitrile such as acetonitrile, at a temperature from about 0°C to around 65°C.

Amines of formula (7) may be formed from 2-halopyridine-3-carbonitriles of formula (8) by reaction with a reagent of formula $\text{HXCH}_2\text{CO}_2\text{Et}$ (where Et is an ethyl group and X is an -O- or -S- atom or a -NH- group). The reaction may be

performed in the presence of a solvent such as a substituted amide, for example *N,N*-dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or an alcohol such as ethanol, in the presence of a base, for example an inorganic base such as sodium carbonate, a hydride, e.g. sodium hydride, or an organic base such as 1,5-diazabicyclo[4.3.0]non-5-ene or a trialkylamine such as triethylamine, at a temperature between about 0°C and 100°C. The carbonitrile starting materials are readily available or may be obtained from known compounds using standard procedures.

The intermediate pyridinones of formula (4) are useful for obtaining other compounds of the invention using standard coupling or displacement reactions.

Thus, for example, palladium-catalysed coupling such as described for the amination above additionally may be generally employed with a pyridinone of formula (2) or (3) [obtainable from compound (4)] and any other amine, amide, urea and other appropriate starting materials $\text{Ar}(\text{CH}_2)_q\text{HetH}$ (including, for example, a starting material of formula ArNHNH_2) to obtain a compound of the invention.

In another example, compounds of formula (1) in which the ArL- group is linked to the remainder of the compound through a carbon atom may be obtained by palladium coupling using a reagent such as tetrakis(triphenylphosphine)palladium(0), an intermediate of formula (2) or (3) [obtainable from compound (4)], a halide $\text{Ar}(\text{CH}_2)_q\text{HetCH}_2\text{Hal}$ (where Hal is a halogen atom such as a bromine atom) or $\text{Ar}(\text{CH}_2)_q\text{CR}^{3a}\text{R}^{3b}\text{Hal}$, and activated zinc, in a solvent such as tetrahydrofuran at an elevated temperature.

In a further example, compounds of formula (1) in which L is a $-\text{S}(\text{CH}_2)_q-$ atom or chain may be obtained by displacement of the bromine atom in a pyridinone of formula (2) or (3) [obtainable from compound (4)] using a thiol $\text{Ar}(\text{CH}_2)_q\text{SH}$ and a base such as potassium carbonate or sodium hydride in a solvent such as *N,N*-dimethylformamide, if necessary at an elevated temperature. Similarly, the bromine atom in a pyridinone of formula (2) or (3) [obtainable from compound (4)] may be displaced using a compound $\text{Ar}(\text{CH}_2)_q\text{OH}$ in the presence of Cu(II)O , a base such as potassium carbonate and a solvent such as pyridine at an elevated temperature, to yield a compound of the invention in which L is a $-\text{O}(\text{CH}_2)_q-$ atom or chain.

In a still further example, compounds of formula (1) in which L is a $-\text{CH}(\text{OH})(\text{CH}_2)_q-$ chain may be obtained by reacting compound (2) or (3) with a base such as *n*-butyllithium or *tert*-butyllithium in a suitable solvent, e.g. tetrahydrofuran, followed by treatment with an aldehyde $\text{Ar}(\text{CH}_2)_q\text{CHO}$.

- 5 In a yet further example, compounds of formula (1) in which L is a $-\text{S}(\text{O})_2\text{NH}(\text{CH}_2)_q-$ chain may be obtained by reacting compound (2) or (3) with a base such as *n*-butyllithium in a suitable solvent, e.g. tetrahydrofuran, then with sulphur dioxide, followed by treatment with a halogenating agent such as *N*-chloro-succinimide, and subsequently with a reagent of formula $\text{Ar}(\text{CH}_2)_q\text{NH}_2$, typically in
10 the presence of pyridine and 4-(dimethylamino)pyridine.

- Compounds of formula (1) in which L is a $-\text{CH}_2\text{CH}_2-$ chain may be obtained from a precursor compound, corresponding to a compound of formula (1) as depicted above in which L represents $-\text{C}\equiv\text{C}-$, by reduction, for example by catalytic hydrogenation whereby the requisite precursor compound is treated with hydrogen in
15 the presence of a hydrogenation catalyst, e.g. palladium on charcoal, in a solvent such as ethanol. The precursor compound may in turn be obtained by reacting a compound of formula (2) or (3) with a compound of formula $\text{Ar}-\text{C}\equiv\text{CH}$ in the presence of a transition metal catalyst, e.g. dichlorobis(triphenylphosphine)-palladium(II), which reaction may conveniently be effected at an elevated
20 temperature in a solvent such as 1,2-dimethoxyethane, typically in the presence of copper(I) iodide and an organic base such as diisopropylethylamine.

- Conditions analogous to those described above for converting a compound of formula (2) or (3) as depicted above into a compound of formula (1) may also be employed for converting a compound of formula (2) or (3) wherein the ethyl ester
25 moiety is replaced by another suitable substituent, e.g. cyano ($-\text{CN}$) or carboxamido ($-\text{CONH}_2$), into the corresponding compound of formula (1) wherein Y is a substituted carbon atom in which the substituent is other than an ethyl ester moiety (e.g. compounds wherein this moiety is $-\text{CN}$ or $-\text{CONH}_2$). The relevant precursors of formula (2) or (3) wherein the ethyl ester moiety is replaced by another suitable
30 substituent, e.g. cyano ($-\text{CN}$) or carboxamido ($-\text{CONH}_2$), may be prepared by the

procedures described in the accompanying Examples, or by methods analogous thereto.

Compounds of formula (1) in which L is a $\text{-NHCO(CH}_2\text{)}_q\text{-}$ chain may be obtained from a precursor compound, corresponding to a compound of formula (1) as depicted above in which -LAr represents -NH_2 , by reaction with an acylating agent of formula $\text{Ar(CH}_2\text{)}_q\text{C(O)Hal}$ (wherein Hal represents a halogen atom, e.g. chloro), which reaction is conveniently effected in the presence of an organic base such as triethylamine, 4-(dimethylamino)pyridine, and a solvent such as dichloromethane.

Compounds of formula (1) in which L is a $\text{-NHSO}_2\text{(CH}_2\text{)}_q\text{-}$ chain may be obtained from a precursor compound, corresponding to a compound of formula (1) as depicted above in which -LAr represents -NH_2 , by reaction with a compound of formula $\text{Ar(CH}_2\text{)}_q\text{S(O)}_2\text{Hal}$ (wherein Hal represents a halogen atom, e.g. chloro), which reaction is conveniently effected in the presence of a strong base such as sodium hydride, in a solvent such as *N,N*-dimethylformamide.

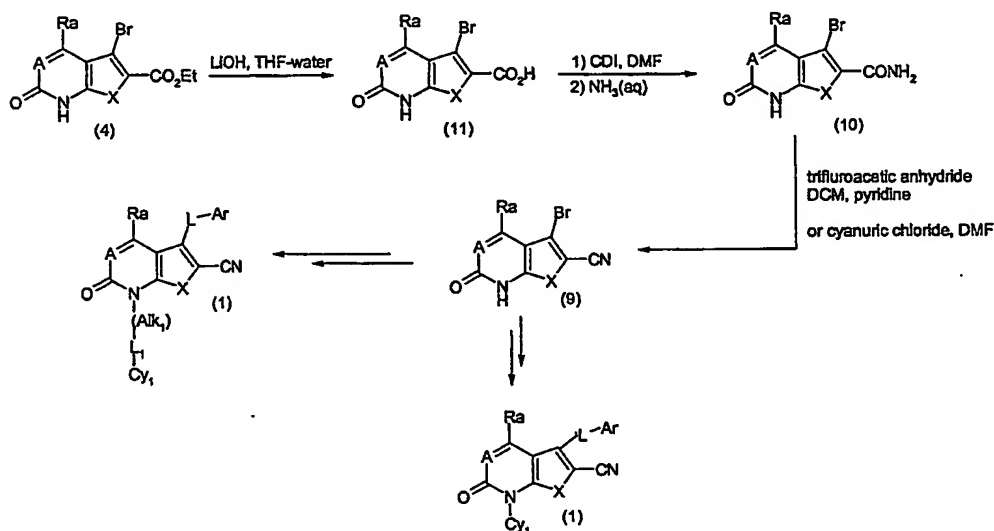
Compounds of formula (1) in which L is a $\text{-NHCONH(CH}_2\text{)}_q\text{-}$ chain may be obtained from a precursor compound, corresponding to a compound of formula (1) as depicted above in which -LAr represents -NH_2 , by reaction with phosgene in a suitable solvent, e.g. a mixture of toluene and dichloromethane, typically at a temperature in the region of 0°C , followed by reaction with an amine of formula $\text{Ar(CH}_2\text{)}_q\text{NH}_2$, which reaction is conveniently effected in the presence of an organic base such as triethylamine.

The precursor compound referred to immediately above, corresponding to a compound of formula (1) as depicted above in which -LAr represents -NH_2 , may be obtained by reacting a dialkyluracil, e.g. 1,3-dimethyluracil, with a compound of formula $\text{Cy}^1\text{L}^1(\text{Alk}^1)_n\text{NHC(S)CH}_2\text{CN}$, which reaction may conveniently be accomplished in the presence of a base, e.g. sodium methoxide, typically in an alkanol solvent, for example a methanol/ethanol mixture; the 3-cyano-6-oxo-1,6-dihydropyridine-2-thiolate intermediate thereby obtained can then be transformed into the desired precursor compound referred to above by treatment with a compound of formula $\text{Hal-CH}_2\text{-R}^{10}$ [in which Hal represents a halogen atom, e.g. chloro or

bromo, and $-C(R^{10})=$ corresponds to the moiety Y as defined above], typically in a solvent such as acetonitrile or ethanol.

In another process according to the invention, a compound of formula (1) in which A is a $-C(R^b)=$ group, X is an -O- or -S- atom or a -NH- group and Y is a $-C(CN)=$ group may be prepared using the reactions set out in Scheme 2 below:

Scheme 2



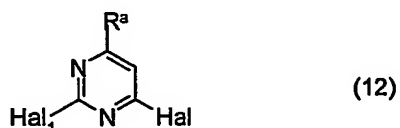
10

Thus, in Scheme 2, a 2-cyano intermediate of formula (9) may be converted in a final step to a compound of the invention using the reactions and reagents described above in relation to the conversion of intermediates of formula (4) to compounds of the invention. Nitriles of formula (9) may be obtained by dehydration of the corresponding amide of formula (10) using a dehydrating agent such as trifluoroacetic anhydride in the presence of a base such as pyridine in a solvent, for example a halogenated hydrocarbon such as dichloromethane, at around ambient temperature. Alternatively, cyanuric chloride may be used in a solvent such as N,N -dimethylformamide at a temperature from around $0^\circ C$ to $110^\circ C$. Amides of formula (10) may be obtained from the corresponding acids of formula (11) using conventional procedures, for example by reaction with 1,1'-carbonyldiimidazole and

20

aqueous ammonia in a solvent such as *N,N*-dimethylformamide at ambient temperature. The intermediate acids of formula (11) may be prepared by hydrolysis of esters of formula (4) using a base such as lithium hydroxide in water and a solvent such as tetrahydrofuran.

- 5 Compounds of formula (1) in which A is a -N= atom may be obtained using the synthetic routes in Schemes (1) and (2) with a pyrimidine starting material of formula (12):



10

wherein Hal₁ and Hal, which may be the same or different, is each a halogen atom such as a chlorine atom.

- In this instance the final step in the synthesis of a compound of the invention may be hydrolysis of the Hal₁ atom using a base such as sodium hydroxide or
- 15 potassium hydroxide in a solvent such as an alcohol, e.g. methanol or ethanol, at an elevated temperature, e.g. the reflux temperature. Alternatively, the Hal₁ atom may first be converted to an ether by reaction with an alkoxide such as sodium methoxide or sodium benzyloxide in a solvent, e.g. an alcohol such as methanol or ethanol, at a temperature between 0°C and the reflux temperature, and the ether then cleaved
- 20 using standard procedures such as by reduction with hydrogen gas in the presence of a catalyst such as a palladium catalyst, e.g. palladium on charcoal, or, where the ether is an alkyl ether, by reaction with a trialkylsilyl halide such as trimethylsilyl chloride, optionally in the presence of an inorganic halide such as sodium iodide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, or in a nitrile, e.g.
- 25 acetonitrile.

Compounds of the invention and intermediates thereto where A represents a -N(R^b)- or -C(R^b)(R^c)- group may be generated from corresponding compounds of

the invention or intermediates thereto where A represents a $-N=$ or $-C(R^b)=$ group by reduction, for instance by catalytic hydrogenation using a metal catalyst such as palladium on charcoal in the presence of hydrogen gas at an elevated pressure in a solvent such as an alcohol, e.g. ethanol, optionally at an elevated temperature, e.g.
5 between 40°C and 60°C.

Where in the general processes described above intermediates such as alkylating agents of formula $Cy^1L^1(Alk^1)_nZ$, reagents of formula $HXCH_2CO_2Et$ and any other intermediates required in the synthesis of compounds of the invention are not available commercially or known in the literature, they may be readily obtained
10 from simpler known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to
15 obtain or modify other intermediates and in particular compounds of formula (1) where appropriate functional groups exist in these compounds.

Thus, for example, aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as *n*-butyllithium or *tert*-butyllithium, optionally at a low temperature, e.g. around
20 -78°C, in a solvent such as tetrahydrofuran, and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using *N,N*-dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile, an alcohol group may be introduced by using an aldehyde as the electrophile, and an acid may be
25 introduced by using carbon dioxide as the electrophile. Aromatic acids of formula $ArCO_2H$ may also be generated by quenching Grignard reagents of formula $ArMgHal$ with carbon dioxide.

Aromatic acids of formula $ArCO_2H$ generated by this method and acid-containing compounds in general may be converted to activated derivatives, e.g. acid
30 halides, by reaction with a halogenating agent such as a thionyl halide, e.g. thionyl chloride, a phosphorus trihalide such as phosphorus trichloride, or a phosphorus

pentahalide such as phosphorus pentachloride, optionally in an inert solvent such as an aromatic hydrocarbon, e.g. toluene, or a chlorinated hydrocarbon, e.g.

dichloromethane, at a temperature from about 0°C to the reflux temperature, or may

be converted into Weinreb amides of formula $\text{ArC}(\text{O})\text{N}(\text{OMe})\text{Me}$ by conversion to

- 5 the acid halide as just described and subsequent reaction with an amine of formula $\text{HN}(\text{OMe})\text{Me}$ or a salt thereof, optionally in the presence of a base such as an organic amine, e.g. triethylamine, in an inert solvent such as an aromatic hydrocarbon, e.g. toluene, or a chlorinated hydrocarbon, e.g. dichloromethane, at a temperature from about 0°C to ambient temperature.

- 10 Acid ($-\text{CO}_2\text{H}$) groups in the compounds of the invention or intermediates thereto may be transformed into amide ($-\text{CONH}_2$) groups by treatment with ammonia in the presence of a condensing agent, for example 1,1'-carbonyldiimidazole, typically in a solvent such as *N,N*-dimethylformamide.

- Compounds of the invention and intermediates thereto may be prepared by
15 alkylation, arylation or heteroarylation. For example, compounds containing a $-\text{L}^1\text{H}$ group (where L^1 is a linker atom or group) may be treated with an alkylating agent Cy^1Z^2 in which Z^2 is a leaving atom or group such as a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy, or arylsulphonyloxy, e.g. *p*-
20 toluenesulphonyloxy, group.

- The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium carbonate or potassium carbonate, an alkoxide, e.g. potassium *tert*-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as *N,N*-dimethylformamide, or an ether, e.g. a
25 cyclic ether such as tetrahydrofuran.

- In another example, compounds containing a $-\text{L}^2\text{H}$ group as defined above may be functionalised by acylation or thioacylation, for example by reaction with the alkylating agents just described but in which Z^2 is replaced by a $-\text{C}(\text{O})\text{Z}^3$, $-\text{C}(\text{S})\text{Z}^3$, $-\text{N}(\text{R}^2)\text{C}(\text{O})\text{Z}^3$ or $-\text{N}(\text{R}^2)\text{C}(\text{S})\text{Z}^3$ group in which Z^3 is a leaving atom or group as
30 described for Z^2 . The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride, or an amine, e.g. triethylamine or *N*-methylmorpholine,

in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride, or an amide, e.g. *N,N*-dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for example one of the alkylating agents described above in
5 which Z^2 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or *N,N'*-dicyclohexylcarbodiimide, or a benzotriazole such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, advantageously in the presence of a catalyst such as a *N*-hydroxy compound, e.g. a *N*-hydroxytriazole such as 1-
10 hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethyl chloroformate, prior to the desired acylation reaction

In a further example, compounds may be obtained by sulphonylation of a compound containing an $-OH$ group by reaction with one of the above alkylating agents but in which Z^2 is replaced by a $-S(O)Hal$ or $-SO_2Hal$ group (in which Hal is a
15 halogen atom such as chlorine atom) in the presence of a base, for example an inorganic base such as sodium hydride, in a solvent such as an amide, e.g. a substituted amide such as *N,N*-dimethylformamide, at for example ambient temperature.

In another example, compounds containing a $-L^2H$ group as defined above
20 may be coupled with one of the alkylation agents just described but in which Z^2 is replaced by an $-OH$ group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine, and an activator such as diethyl, diisopropyl or dimethyl azodicarboxylate.

Ester groups such as $-CO_2Alk^6$ and $-CO_2R^4$ in the compounds of formula (1)
25 and intermediates thereto may be converted to the corresponding acid ($-CO_2H$) by acid- or base-catalysed hydrolysis depending on the nature of the group Alk^6 or R^4 . Acid- or base-catalysed hydrolysis may be achieved, for example, by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid, in an organic solvent, e.g. dichloromethane, or a mineral acid such as hydrochloric acid in a solvent such as
30 1,4-dioxane, or an alkali metal hydroxide, e.g. lithium hydroxide or sodium hydroxide, in an aqueous alcohol, e.g. aqueous methanol or aqueous ethanol.

In a further example, $-OR^6$ (where R^6 represents an alkyl group such as methyl) in compounds of formula (1) and intermediates thereto may be cleaved to the corresponding alcohol $-OH$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at a low temperature, e.g. around
5 $-78^\circ C$.

Alcohol $(-OH)$ groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{31}$ group (where R^{31} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon, in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around
10 ambient temperature to the reflux temperature. In another example, $-OH$ groups may be generated from the corresponding ester (e.g. $-CO_2Alk^6$) or aldehyde $(-CHO)$ by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, $-OH$ groups in the compounds may be converted to a
15 corresponding $-OR^6$ group by coupling with a reagent R^6OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl or dimethyl azodicarboxylate.

Aminosulphonylamino $(-NHSO_2NH_2)$ groups in the compounds may be obtained, in another example, by reaction of a corresponding amine $(-NH_2)$ with
20 sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example, compounds containing a $-NHCSR^7$ or $-CSNHR^7$ group may be prepared by treating a corresponding compound containing a $-NHCOR^7$ or $-CONHR^7$ group with a thiation reagent, such as Lawesson's Reagent or P_2S_5 , in an
25 anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example, amine $(-NH_2)$ groups may be alkylated using a reductive alkylation process employing an aldehyde and a reducing agent. Suitable reducing agents include borohydrides, for example sodium triacetoxyborohydride or sodium
30 cyanoborohydride. The reduction may be carried out in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an

alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Alternatively, the amine and aldehyde may be initially reacted in a solvent such as an aromatic hydrocarbon, e.g. toluene, and then subjected to hydrogenation in the presence of a metal catalyst, for example palladium on a

5 support such as carbon, in a solvent such as an alcohol, e.g. ethanol.

Amine (-NH₂) groups in the compounds of the invention or intermediates thereto may generally be transformed into halogen atoms, e.g. bromo, by treatment with a nitrite reagent, e.g. *tert*-butyl nitrite, in the presence of a copper(II) halide, e.g. copper(II) bromide, typically in a solvent such as acetonitrile.

10 In a further example, amine (-NH₂) groups in compounds of formula (1) and intermediates thereto may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol, at ambient temperature.

In another example, a nitro (-NO₂) group may be reduced to an amine (-NH₂),
15 for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, in a solvent such as an ether, e.g. tetrahydrofuran, or an alcohol, e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

20 In a further example, amine (-CH₂NH₂) groups in compounds of formula (1) and intermediates thereto may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney[®] nickel, in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, or an
25 alcohol, e.g. methanol or ethanol, optionally in the presence of ammonia solution at a temperature from ambient temperature to the reflux temperature, or by chemical reduction using for example a metal hydride, e.g. lithium aluminium hydride, in a solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran, at a temperature from 0°C to the reflux temperature.

30 In another example, sulphur atoms in the compounds, for example when present in a group L, L¹ or L², may be oxidised to the corresponding sulfoxide or

sulphone using an oxidising agent such as a peroxyacid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

5 In a further example, *N*-oxides of compounds of formula (1) may in general be prepared for example by oxidation of the corresponding nitrogen base as described above in relation to the preparation of intermediates of formula (5).

Salts of compounds of formula (1) may be prepared by reaction of compounds of formula (1) with an appropriate base in a suitable solvent or mixture of solvents, e.g. an organic solvent such as an ether, e.g. diethyl ether, or an alcohol, 10 e.g. ethanol, using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by 15 reaction of a mixture of enantiomers of formula (1), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

20 In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an 25 ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

30 The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

- NMM - *N*-methylmorpholine; EtOAc - ethyl acetate;
 MeOH - methanol; BOC - *tert*-butoxycarbonyl;
 DCM - dichloromethane; AcOH - acetic acid;
 5 DIPEA - diisopropylethylamine; EtOH - ethanol;
 Pyr - pyridine; Ar - aryl;
 DMSO - dimethylsulphoxide; iPr - isopropyl;
 Et₂O - diethyl ether; Me - methyl;
 THF - tetrahydrofuran; h - hour;
 10 MCPBA - 3-chloroperoxybenzoic acid; NBS - *N*-bromosuccinimide;
 FMOC - 9-fluorenylmethoxycarbonyl; r.t. - room temperature;
 DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene;
 CDI - 1,1'-carbonyldiimidazole; DMAP - 4-(dimethylamino)pyridine;
 EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride;
 15 HOBT - 1-hydroxybenzotriazole hydrate;
 BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;
 DMF - *N,N*-dimethylformamide; MTBE - *tert*-butyl methyl ether;
 DME - ethylene glycol dimethyl ether.

20 All NMRs were obtained either at 300 MHz or 400 MHz.

Compounds were named with the aid of either Beilstein Autonom, supplied by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany, or ACD Labs Name (v. 5.0 or v. 6.0), supplied by Advanced Chemical Development, Toronto, Canada.

25 LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following method: Phenomenex Luna 3 μ C₁₈(2) 50 x 4.6 mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of 0.9 mlmin⁻¹; column temperature 40°C.

30

Gradient:

Time (min)	%B
Initial	5
2.0	95
3.0	95
5.0	5
5.5	end

Where stated, alternative LCMS conditions (Conditions B) were used:

- 5 LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100/ThermoFinnigan LCQ Duo LC/MS system using Electrospray ionisation and the following LC method: Phenomenex Luna C₁₈(2) 5 μ 100 mm x 4.6 mm column; mobile phase A = 0.08% formic acid in water; mobile phase B = 0.08% formic acid in MeCN; flow rate of 3.0 mlmin⁻¹; column temperature 35°C.

10

Gradient:

Time (min)	%A	%B
0.00	95.0	5.0
4.40	5.0	95.0
5.30	5.0	95.0
5.32	95.0	5.0
6.50	95.0	5.0

INTERMEDIATE 1

15

Ethyl 3-aminothienof[2,3-*b*]pyridine-2-carboxylate

A mixture of 2-chloro-3-cyanopyridine (330 g), ethyl 2-mercaptoacetate (361.2 g), sodium carbonate (265 g) and EtOH (1.2 l) was heated to reflux for 4.5 hours. It was then cooled to ambient temperature, added to water (10 l) and the

addition was washed with water (5 l). The resulting slurry was stirred for 30 minutes and then it was filtered. The filter cake was washed with two portions of water (2 x 2.5 l) and dried at the pump. The solids were then dried to constant weight under vacuum at 45°C to yield the *title compound* as a brown solid (493.1 g, 93.2%). δ_{H} (CDCl₃) 8.68 (1H, dd, *J* 4.7, 1.2 Hz), 7.93 (1H, dd, *J* 8.5, 1.2 Hz), 7.29 (1H, dd, *J* 8.5, 4.7 Hz), 5.90 (2H, b), 4.38 (2H, q, *J* 7.0 Hz), 1.40 (3H, t, *J* 7.0 Hz). LCMS RT 2.9 minutes, 223 (M+H)⁺.

INTERMEDIATE 2

10

Ethyl 3-bromothieno[2,3-*b*]pyridine-2-carboxylate

Intermediate 1 (363.6 g) was added in portions over two hours to a mixture of copper(II) bromide (403.3 g), *tert*-butyl nitrite (220.6 g) and acetonitrile (3.6 l) stirred at a temperature of 20 to 25°C. The mixture was stirred at 20°C for 2 hours before it was slowly added to 2M HCl(aq) (4.2 l). The reaction mixture slurry was filtered and the solids were washed with water (500 ml). The combined filtrate was extracted with ethyl acetate (8 l), and this ethyl acetate solution was washed with 2M HCl(aq) (2.2L). The solids were dissolved in ethyl acetate (6 l), and this solution was washed twice with 2M HCl(aq) (4.4 l and 2.2 l). The two ethyl acetate solutions were then combined and washed with 2M HCl(aq) (2.2 l) and twice with water (2 x 2 l). The ethyl acetate solution was then dried (MgSO₄), filtered and concentrated *in vacuo* at 40 mbar and 60°C to give a solid residue. This was broken up and dried to constant weight under vacuum at 45°C to yield the *title compound* as a brown solid (458.5 g, 97.9%). δ_{H} (DMSO-*d*₆) 8.89 (1H, d, *J* 4.7 Hz), 8.47 (1H, d, *J* 8.6 Hz), 7.71 (1H, dd, *J* 8.6, 4.7 Hz), 4.46 (2H, q, *J* 7.2 Hz), 1.40 (3H, t, *J* 7.2 Hz). LCMS RT 3.8 minutes, 288 (M+H)⁺.

30

INTERMEDIATE 3

Ethyl 3-Bromothieno[2,3-*b*]pyridine-2-carboxylate *N*-oxide

To a slurry of Intermediate 2 (214 g, 0.747 mol) in DCM (2140 ml) under
5 nitrogen was added MCPBA (240 g @ 70% = 168 g, 0.97 mol) portionwise over 0.5
h. The reaction was then stirred at room temperature for 18h. The reaction mixture
was quenched with water (800 ml) and the pH adjusted to 8.5 with 10% w/v sodium
carbonate solution (1250 ml). The basic aqueous layer was removed and the organic
layer washed with water until pH 7. The organic layer was concentrated *in vacuo*
10 and the crude *title product* was recovered as a tan solid. The crude product was
purified by slurrying in MTBE (600 ml) for 1 h at 0-5°C to give the *title compound*
(174 g, 77%). δ_H (CDCl₃) 8.44 (1H, dd, *J* 6.2, 0.8 Hz), 7.87 (1H, dd, *J* 8.3, 0.8 Hz),
7.48 (1H, dd, *J* 8.3, 6.2 Hz), 4.49 (2H, q, *J* 7.1 Hz), 1.48 (3H, t, *J* 7.1 Hz). LCMS
(ES⁺) RT 2.61 minutes, 302 (M+H)⁺.

15

INTERMEDIATE 4

Ethyl 3-bromo-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 3 (500 mg, 1.66 mmol) and DMF (10 ml) was set
20 to stir at 0°C under nitrogen. To this reaction mixture was added trifluoroacetic
anhydride (3.49 g, 2.36 ml, 16.6 mmol) in one portion via syringe. After stirring for
16 hours the volatiles were removed *in vacuo* and the residue co-evaporated with
toluene (2 x 20 ml). The crude material was then extracted with EtOAc (2 x 100 ml).
The EtOAc extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude
25 product was purified by a re-slurry in toluene (10 ml) to give the *title compound* as a
beige solid (260 mg, 52%). δ_H (DMSO-*d*₆) 12.20 (1H, br s), 7.75 (1H, d, *J* 9.0 Hz),
6.50 (1H, d, *J* 9.0 Hz), 4.15 (2H, q, *J* 7.1 Hz), 1.12 (3H, t, *J* 7.1 Hz). LCMS (ES⁺)
RT 2.86 minutes, 302 ((M+H)⁺, 100%). MP = 261.7-268.1°C.

30

INTERMEDIATE 5

Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

To a 2-necked round-bottomed flask was added in sequence Intermediate 4
5 (302 mg, 1.00 mmol), copper(II) acetate (278 mg, 1.50 mmol), phenylboronic acid
(488 mg, 4.00 mmol), DCM (5 ml) and pyridine (158 mg, 2.00 mmol). The reaction
was stirred at room temperature for 18 h with the exclusion of moisture. The
reaction was then diluted with DCM (50 ml), washed with 2M HCl(aq) (50ml), and
the aqueous was re-extracted with DCM (50 ml). The combined organics were then
10 washed with water (50 ml), dried (MgSO₄) and concentrated *in vacuo*. The crude
product was purified by a slurry in methanol (12 ml), to give the *title compound* as a
beige solid (270 mg, 72%). δ_H (CDCl₃) 7.82 (1H, d, *J* 8.5 Hz), 7.70-7.62 (3H, m),
7.54-7.42 (2H, m), 6.70 (1H, d, *J* 8.5 Hz), 4.15 (2H, q, *J* 7.1 Hz), 1.14 (3H, t, *J* 7.1
Hz). LCMS (ES⁺) RT 3.75 minutes, 378 (M+H)⁺. MP = 201.6-206.0°C.

15

INTERMEDIATE 6

Sodium 3-cyano-6-oxo-1-phenyl-1,6-dihydropyridine-2-thiolate

A solution of sodium methoxide in MeOH (30 wt %, 202.2 g) was added to
20 absolute EtOH (360 ml), followed by 1,3-dimethyluracil (75 g) and 2-cyano-*N*-
phenylthioacetamide (Adhikari *et al.*, *Australian J. Chem.*, 1999, **52**, 63-67) (90 g).
The resulting mixture was heated at reflux for 8 h and then allowed to cool to
ambient temperature overnight. The reaction mixture was then cooled to +5°C and
maintained at this temperature for at least an hour when the product was recovered
25 by filtration. The filter cake was washed with cold (+5°C) absolute ethanol (450 ml)
and then dried to constant weight under vacuum at 45°C to give the *title compound*
as a pale pink solid (130.0 g). The product thus obtained contained residual EtOH
and MeOH, estimated at 12.2 wt % by ¹H nmr, corresponding to a corrected yield of
114.1 g. δ_H (DMSO-*d*₆) 7.32 (2H, m), 7.27-7.18 (1H, m), 7.16 (1H, d, *J* 9.1 Hz),

6.92 (2H, m), 5.63 (1H, d, J 9.1 Hz). LCMS (Conditions B) (ES^+) RT 2.43 minutes, 229 ($M+H$) $^+$.

INTERMEDIATE 7

5

3-Amino-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

A mixture of Intermediate 6 (100 g at 100%) and chloroacetonitrile (30.4 ml) in acetonitrile (500 ml) was heated at reflux for 2 h. The mixture was cooled, initially to 40°C when water (300 ml) was added, and then to +10°C. The reaction
10 was maintained at +10°C for at least 1h when the product was recovered by filtration. The filter cake was washed with cold (+10°C) water (500 ml) followed by a cold (+10°C) mixture of acetonitrile and water (1:1, 300 ml). The product was dried under vacuum at 50°C to constant weight to give the *title compound* as an off-white solid (100.9 g). δ_H (DMSO- d_6) 7.90 (1H, d, J 9.6 Hz), 7.46-7.33 (3H, m), 7.25
15 (2H, m), 6.95 (2H, br s), 6.35 (1H, d, J 9.6 Hz). LCMS (Conditions B) (ES^+) RT 2.69 minutes, 268 ($M+H$) $^+$.

INTERMEDIATE 8

20 3-Amino-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid ethyl ester

A mixture of Intermediate 6 (0.34 g at 100%) and ethyl bromoacetate (0.197 ml) in ethanol (6 ml) was stirred at room temperature for 1 h. Water (10 ml) was
then added. The solid was filtered and washed with more water (2 ml). The product
25 was dried under vacuum at 40°C to constant weight to give the *title compound* as a pale pink solid (0.35 g). δ_H (DMSO- d_6) 8.2 (1H, d, J 9.6 Hz), 7.6 (3H, m), 7.45 (2H, m), 7.15 (2H, br s), 6.55 (1H, d, J 9.6 Hz), 4.15 (2H, q, J 7.1 Hz), 1.2 (3H, t, J 7.1 Hz). LCMS (Conditions B) (ES^+) RT 3.29 minutes, 315 ($M+H$) $^+$.

INTERMEDIATE 9

3-Bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

To a mixture of anhydrous copper(II) bromide (23.4 g) and *tert*-butyl nitrite
5 (14.8 ml) in acetonitrile (600 ml), at room temperature, was added Intermediate 7 (20
g) portionwise, at such a rate as to keep the internal temperature below 25°C. The
addition took approximately 1 hour. Analysis by HPLC indicated almost complete
conversion of starting material after a further 30 minutes of stirring. The reaction
mixture was then poured onto 500 ml of 1M HCl (N.B. caution, brown fumes given
10 off). This was then extracted with dichloromethane (2 x 400 ml). The combined
organic extracts were then washed with 1M HCl (3 x 300 ml), dried over MgSO₄ and
evaporated to dryness. The resulting crude product was then recrystallised from
methyl isobutyl ketone (700 ml). The product was dried under vacuum at 50°C to
constant weight to give the *title compound* as a light brown solid (15.14 g). δ_{H}
15 (CDCl₃) 7.75 (1H, d, *J* 8.5 Hz), 7.55-7.70 (3H, m), 7.35 (2H, m), 6.80 (1H, d, *J* 8.5
Hz). LCMS (Conditions B) (ES⁺) RT 3.54 minutes, no parent ion observed.

INTERMEDIATE 10

3-Bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

Sodium hydroxide (1.83 g, 45.8 mmol, 1.1 equiv.) was added to a suspension
of Intermediate 5 (15.75 g, 41.6 mmol, 1.0 equiv.) in ethanol (78 ml) and water (78
ml) at room temperature. The reaction mixture was then heated to reflux. Once
reflux was attained the solid material had gone into solution and analysis by HPLC
25 indicated complete conversion to the acid. The reaction mixture was then cooled to
~70°C and c. hydrochloric acid (46 ml) added over a 10 minute period. The reaction
was allowed to cool to room temperature and the resultant solid collected by
filtration, washed with water (3 x 25 ml) and dried *in vacuo* to give the *title*
compound as a beige solid (13.81 g, 97%). δ_{H} (DMSO-*d*₆) 8.13 (1H, d, *J* 9.6 Hz),
30 7.92-7.80 (3H, m), 7.78-7.74 (2H, m), 6.92 (1H, d, *J* 9.6 Hz).

INTERMEDIATE 11**3-Bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide**

CDI (530 mg, 3.27 mmol) was added to a solution of Intermediate 10 (800
5 mg, 2.29 mmol) in DMF (15 ml). After 10 min, ammonia (25% solution) (5 ml) was
added and the reaction mixture stirred at r.t. for 4 h. The solvent was removed *in*
vacuo and the residue acidified with 2M HCl and extracted with DCM (x 3). The
combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to give
the *title compound* as a white solid (600 mg, 75%). δ_{H} (DMSO-*d*₆) 6.67 (1H, d, *J* 9.6
10 Hz), 7.7-7.5 (5H, m), 7.85 (1H, d, *J* 9.6 Hz). LCMS (ES⁺) RT 2.69 minutes, 349
(M+H)⁺.

INTERMEDIATE 12

15 **Ethyl 6-oxo-7-phenyl-3-(phenylethynyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-**
carboxylate

A mixture of Intermediate 5 (756 mg, 2.0 mmol), dichlorobis(triphenyl-
phosphine)palladium(II) (140 mg, 0.2 mmol) and Cu(I)I (190 mg, 1.0 mmol) was
suspended in DME (10 ml) and diisopropylethylamine (1.5 ml, 10 mmol) added.
20 Phenylacetylene (0.33 ml, 3.2 mmol) was added dropwise and the black solution
heated at 75°C for 18 h. The reaction mixture was cooled to r.t., and the solvents
removed *in vacuo*. The crude residue was purified by chromatography on silica (0-
20% EtOAc in hexanes) to give the *title compound* as a white solid (430 mg, 54%).
 δ_{H} (CDCl₃) 7.95 (1H, d, *J* 9.5 Hz), 7.60-7.49 (5H, m), 7.37-7.31 (5H, m), 6.67 (1H,
25 d, *J* 9.5 Hz), 4.28 (2H, q, *J* 7.2 Hz), 1.29 (3H, t, *J* 7.2 Hz). LCMS (ES⁺) RT 4.15
minutes, 400 (M+H)⁺.

INTERMEDIATE 13**Ethyl 3-bromo-7-(cyclopropylmethyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate**

- 5 Sodium hydride (60% in mineral oil) (3.27 g, 81.4 mmol) was added in portions to a solution of Intermediate 4 (22.3 g, 74 mmol) in DMF (300 ml) at 0°C. The mixture was stirred at r.t. for 30 min then cyclopropylmethyl bromide (10 g, 74 mmol) was added slowly and the mixture heated at 60°C overnight. The DMF was removed *in vacuo* and the residue partitioned between EtOAc and brine. The organic
- 10 phase was dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (silica, 0% to 10% EtOAc in DCM) gave the *title compound* as a yellow solid (12.5 g, 47%). δ_H (CDCl₃) 7.57 (1H, d, *J* 9.5 Hz), 6.47 (1H, d, *J* 9.5 Hz), 4.22 (2H, q, *J* 7.0 Hz), 3.87 (2H, d, *J* 7.1 Hz), 1.26-1.19 (4H, m), 0.43-0.37 (4H, m). LCMS (ES⁺) RT 3.80 minutes, 357 (M+H)⁺.

15

EXAMPLE 1**Ethyl 3-(benzylamino)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate**

- 20 Tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.0133 mmol, 5 mol %) was added to a mixture of Intermediate 5 (100 mg, 0.265 mmol), caesium carbonate (120 mg, 0.37 mmol), benzylamine (0.035 ml, 0.32 mmol) and BINAP (17 mg, 0.027 mmol, 10 mol %) in anhydrous toluene (2 ml) and the reaction heated to reflux under nitrogen for 18 h. Solvent was removed *in vacuo* and the crude residue purified by
- 25 chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a white solid (52 mg). δ_H (CDCl₃) 7.80 (1H, br s), 7.72 (1H, d, *J* 9.9 Hz), 7.60-7.48 (3H, m), 7.28-7.10 (7H, m), 6.37 (1H, d, *J* 9.9 Hz), 4.73 (2H, br d, *J* 4.5 Hz), 4.14 (2H, q, *J* 7.1 Hz), 1.18 (3H, t, *J* 7.1 Hz). LCMS (ES⁺) RT 4.03 minutes, 405 (M+H)⁺.

30

EXAMPLES 2 TO 4

General procedure for the preparation of ethyl 3-benzylamino-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylates

- 5 The compounds of Examples 2-4 were prepared by parallel synthesis using a Radleys Carousel reaction station (Radleys Ltd., Saffron Walden, U.K.) following a procedure similar to that described for Example 1. Therefore, to each oven dried reaction tube in the Carousel was added a magnetic stirrer, the appropriate substituted aniline or benzylamine (0.64 mmol), anhydrous toluene (3 ml),
- 10 Intermediate 5 (200 mg, 0.53 mmol), caesium carbonate (240 mg, 0.74 mmol) and tris(dibenzylideneacetone)dipalladium(0) (48 mg, 0.053 mmol, 10 mol %). The reactions were heated to reflux under nitrogen and with magnetic stirring for 48 h. Each reaction was then diluted with DCM (10 ml), washed with water (10 ml), dried (MgSO₄) and concentrated *in vacuo*. The crude products were purified on silica
- 15 eluting with 0-20% EtOAc in DCM to give the *title compounds* as solids.

EXAMPLE 2

Ethyl 3-(*N*-benzyl-*N*-methylamino)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

- 20 From *N*-benzylmethylamine to give the *title compound* (95 mg). δ_H (CDCl₃) 7.73 (1H, d, *J* 9.6 Hz), 7.58-7.41 (3H, m), 7.36-7.14 (7H, m), 6.52 (1H, d, *J* 9.6 Hz), 4.43 (2H, s), 4.17 (2H, q, *J* 7.1 Hz), 2.89 (3H, s), 1.21 (3H, t, *J* 7.1 Hz). LCMS (ES⁺) RT 4.19 minutes, 419 (M+H)⁺.
- 25

EXAMPLE 3

Ethyl 6-oxo-7-phenyl-3-[(1-phenylethyl)amino]-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

- 30 From α -methylbenzylamine to give the *title compound* (149 mg). δ_H (CDCl₃) 7.83 (1H, bd, *J* 7.6 Hz), 7.58 (1H, d, *J* 9.9 Hz), 7.54-7.36 (3H, m), 7.32-7.14 (7H, m),

6.27 (1H, d, J 9.9 Hz), 4.98 (1H, quintet, J 6.8 Hz), 4.18 (2H, q, J 7.1 Hz), 1.58 (3H, d, J 6.8 Hz), 1.21 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 4.19 minutes, 419 ($M+H$) $^+$.

EXAMPLE 4

5

Ethyl 3-[(2,6-difluorobenzyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-
b]pyridine-2-carboxylate

From 2,6-difluorobenzylamine to give the *title compound* (130 mg). δ_H ($CDCl_3$) 8.04 (1H, d, J 9.9 Hz), 7.61-7.40 (3H, m), 7.39-7.25 (3H, m), 7.38-7.14 (1H, m), 6.93-6.78 (2H, m), 6.54 (1H, d, J 9.9 Hz), 4.73 (2H, d, J 6.0 Hz), 4.10 (2H, q, J 7.1 Hz), 1.15 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.98 minutes, 441 ($M+H$) $^+$.

EXAMPLE 5

15 Ethyl 3-benzyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Benzyl bromide (0.040 ml, 0.317 mmol) was added to activated zinc powder (26 mg, 0.397 mmol) in anhydrous THF (2 ml) under nitrogen and the mixture heated to reflux for 2 h. The reaction was cooled to r.t. and Intermediate 5 (100 mg, 0.265 mmol) and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol, 10
20 mol %) added to the reaction mixture. The reaction was then heated to reflux for 18 h with two further portions of $Pd(PPh_3)_4$ (30 mg) added at intervals during the reaction. The reaction was partitioned between EtOAc and water and the EtOAc extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a
25 white solid (87 mg). δ_H ($CDCl_3$) 7.69 (1H, d, J 9.6 Hz), 7.67-7.30 (3H, m), 7.25-7.18 (2H, m), 7.20-7.00 (5H, m), 6.51 (1H, d, J 9.6 Hz), 4.51 (2H, s), 4.21 (2H, q, J 7.2 Hz), 1.22 (3H, t, J 7.2 Hz). LCMS (ES^+) RT 3.92 minutes, 390 ($M+H$) $^+$.

30

EXAMPLE 6Ethyl 6-oxo-3-phenoxy-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 5 (500 mg, 1.32 mmol), phenol (137 mg, 1.46 mmol), Cu(II)O (209 mg, 1.46 mmol) and K₂CO₃ (221 mg, 1.60 mmol) in pyridine (10 ml) was heated at 115°C for 18 h. The reaction was cooled to r.t., 2M HCl(aq) (30 ml) added and the aqueous extracted with EtOAc (3 x 20 ml). The combined EtOAc extracts were washed with 2M HCl(aq), brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-10% EtOAc in DCM) to give the *title compound* as a solid (110 mg). δ_H (CDCl₃) 7.61-7.43 (3H, m), 7.42-7.29 (3H, m), 7.28-7.18 (2H, m), 7.00 (1H, t, *J* 7.4 Hz), 6.92 (2H, d, *J* 7.8 Hz), 6.49 (1H, d, *J* 9.6 Hz), 4.08 (2H, q, *J* 7.1 Hz), 1.04 (3H, t, *J* 7.1 Hz). LCMS (ES⁺) RT 3.81 minutes, 392 (M+H)⁺.

EXAMPLE 7Ethyl 6-oxo-7-phenyl-3-(phenylthio)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 5 (500 mg, 1.32 mmol), benzenethiol (0.15 ml, 1.46 mmol) and K₂CO₃ (221 mg, 1.60 mmol) in DMF (10 ml) was heated at 80°C under nitrogen for 18 h. The reaction was cooled to r.t., diluted with water and the aqueous extracted with EtOAc (3 x 20 ml). The combined EtOAc extracts were washed with water and brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-5% EtOAc in DCM) to give the *title compound* as a solid (150 mg). δ_H (CDCl₃) 7.58-7.48 (3H, m), 7.46 (1H, d, *J* 9.7 Hz), 7.36-7.29 (2H, m), 7.25-7.07 (5H, m), 6.44 (1H, d, *J* 9.7 Hz), 4.21 (2H, q, *J* 7.1 Hz), 1.20 (3H, t, *J* 7.1 Hz). LCMS (ES⁺) RT 3.97 minutes, 408 (M+H)⁺.

EXAMPLE 8Ethyl 6-oxo-7-phenyl-3-[(pyridin-2-ylmethyl)amino]-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

- 5 From Intermediate 5 and 2-(aminomethyl)pyridine by the method of Example 1. White solid. δ_H (CDCl₃) 8.61 (1H, dq, *J* 0.8, 4.9 Hz), 8.21 (1H, br s), 7.81 (1H, d, *J* 9.8 Hz), 7.70 (1H, t, *J* 7.2 Hz), 7.54-7.45 (3H, m), 7.40 (1H, d, *J* 7.5 Hz), 7.28 (2H, m), 7.25 (1H, t, *J* 7.2 Hz), 6.39 (1H, d, *J* 9.8 Hz), 4.94 (2H, s), 4.18 (2H, q, *J* 7.2 Hz), 1.22 (3H, t, *J* 7.2 Hz). LCMS (ES⁺) RT 3.32 minutes, 406 (M+H)⁺.

10

EXAMPLE 93-(Benzylamino)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

- A mixture of tris(dibenzylideneacetone)dipalladium(0) (14 mg, 0.015 mmol, 5 mol %), Intermediate 9 (100 mg, 0.30 mmol), caesium carbonate (137 mg, 0.42 mmol), benzylamine (0.039 ml, 0.36 mmol) and BINAP (19 mg, 0.03 mmol, 10 mol %) in anhydrous toluene (10 ml) was heated at reflux under nitrogen overnight. The mixture was partitioned between DCM and water. The organic phase was dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography on silica (10% EtOAc in DCM) gave the *title compound* as a white solid. δ_H (DMSO-*d*₆) 8.36 (1H, s), 8.03 (1H, d, *J* 9.7 Hz), 7.45-7.38 (3H, m), 7.31-7.29 (2H, m), 7.21-7.19 (4H, m), 7.18-7.08 (1H, m), 6.41 (1H, d, *J* 9.7 Hz), 4.54 (2H, s). LCMS (ES⁺) RT 3.44 minutes, 358 (M+H)⁺.

25

EXAMPLE 106-Oxo-7-phenyl-3-(phenylthio)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

- A mixture of Intermediate 11 (300 mg, 0.86 mmol), K₂CO₃ (143 mg, 1.03 mmol) and benzenethiol (0.106 ml, 1.03 mmol) in DMF (15 ml) was heated at 100°C for 8 h. The reaction was cooled to r.t., concentrated *in vacuo* and azeotroped with heptane (3 x 50 ml). The residue was partitioned between water/DCM and extracted

30

with DCM (2 x 50 ml). The combined DCM extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was triturated with EtOAc (2 x 20 ml) to give the *title compound* as an off-white solid (110 mg, 34%). δ_{H} ($\text{DMSO}-d_6$) 7.90-7.60 (2H, m), 7.50-7.30 (6H, m), 7.25-7.00 (5H, d, J 9.8 Hz), 6.3 (1H, d, J 9.6 Hz).

5 LCMS (ES^+) RT 3.18 minutes, 379 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 11

Ethyl 3-(benzoylamino)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-
10 carboxylate

Triethylamine (0.10 ml, 0.77 mmol), benzoyl chloride (0.10 ml, 0.71 mmol) and DMAP (20 mg) were added to a solution of Intermediate 8 (200 mg, 0.64 mmol) in DCM (5 ml). The reaction was stirred at room temperature for 18 h. The reaction was diluted with DCM (100 ml) and washed with brine. The organics were dried

15 (MgSO_4) and concentrated *in vacuo*. The crude residue was purified by chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a white solid (80 mg, 30%). δ_{H} (CDCl_3) 8.20 (1H, d, J 10.1 Hz), 8.01-7.98 (2H, m), 7.59-7.45 (6H, m), 7.37-7.31 (2H, m), 6.57 (1H, d, J 10.1 Hz), 4.22 (2H, q, J 7.1 Hz), 1.23 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.74 minutes, 419 ($\text{M}+\text{H}$) $^+$.

20

EXAMPLE 12

Ethyl 6-oxo-7-phenyl-3-[(phenylsulphonyl)amino]-6,7-dihydrothieno[2,3-*b*]pyridine-
25 2-carboxylate

Sodium hydride (31 mg of a 60% suspension in mineral oil, 0.77 mmol) was added to a solution of Intermediate 8 (200 mg, 0.64 mmol) in DMF (5 ml). The solution was stirred at room temperature for 10 minutes before benzenesulphonyl chloride (0.10 ml, 0.77 mmol) was added and the reaction mixture then stirred for 18 h. The reaction mixture was poured into brine (50 ml) and extracted with chloroform
30 (3 x 50 ml). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*. The crude residue was purified by chromatography on silica (0-20% EtOAc

in DCM) to give the *title compound* as a white solid (60 mg, 21%). δ_{H} (CDCl_3) 8.75 (1H, br s), 8.25 (1H, d, J 9.8 Hz), 7.60-7.55 (2H, m), 7.51-7.45 (4H, m), 7.38-7.29 (4H, m), 6.64 (1H, d, J 9.8 Hz), 4.05 (2H, q, J 7.1 Hz), 1.05 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.58 minutes, 455 ($\text{M}+\text{H}$) $^+$.

5

EXAMPLE 13

Ethyl 3-[(anilincarbonyl)amino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

- 10 Phosgene (69 mg of a 20% solution in toluene, 0.7 mmol) was added to a solution of Intermediate 8 (200 mg, 0.64 mmol) in toluene (5 ml) and DCM (2 ml) at 0°C and the reaction stirred for 10 minutes. Triethylamine (0.20 ml, 1.54 mmol) and aniline (65 mg, 0.7 mmol) were added and the reaction stirred at room temperature for 18 hours. The reaction was diluted with DCM (100 ml) and washed with brine (2
15 x 100 ml). The organics were dried (MgSO_4) and concentrated *in vacuo*. The crude residue was purified by chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a white solid (152 mg, 55%). δ_{H} ($\text{DMSO}-d_6$) 9.80 (1H, br s), 9.25 (1H, br s), 7.98 (1H, d, J 9.7 Hz), 7.68-7.58 (3H, m), 7.55-7.49 (4H, m), 7.33 (2H, m), 7.03 (1H, m), 6.54 (1H, d, J 9.7 Hz), 4.23 (2H, q, J 7.1 Hz), 1.22 (3H, t, J
20 7.1 Hz). LCMS (ES^+) RT 3.54 minutes, 434 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 14

Ethyl 6-oxo-7-phenyl-3-(2-phenylethyl)-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

- 25 Intermediate 12 (300 mg, 0.75 mmol) was dissolved in EtOAc (100 ml) and 10% palladium on carbon (50 mg) added. A hydrogen atmosphere was applied *via* balloon and the reaction stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by
30 chromatography on silica (10% EtOAc in hexanes) to give the *title compound* as a white solid (120 mg, 39%). δ_{H} (CDCl_3) 7.55-7.46 (4H, m), 7.34-7.31 (2H, m), 7.22-

7.12 (5H, m), 6.52 (1H, d, J 9.7 Hz), 4.22 (2H, q, J 7.1 Hz), 3.32 (2H, m), 2.85 (2H, m), 1.25 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 4.16 minutes, 404 ($M+H$) $^+$.

EXAMPLE 15

5

Ethyl 3-[hydroxy(phenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Intermediate 5 (1.134 g, 3.0 mmol) was dissolved in THF (50ml) under a nitrogen atmosphere and cooled to between -105°C and -111°C. *n*-BuLi (1.32 ml of a 2.5M solution in hexane, 3.3 mmol) was added dropwise. The reaction mixture was stirred for 30 mins at between -105°C and -111°C. A solution of benzaldehyde (0.7 g, 6.6 mmol) in THF (5 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly and then poured into saturated NaHCO₃ solution (50 ml) and extracted with DCM (x 2). The combined DCM
10 extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (Et₂O) to give the *title compound* as an off-white solid (856 mg, 70%). δ_H (CDCl₃) 7.96 (1H, d, J 10 Hz), 7.52-7.70 (3H, m), 7.25-7.50 (7H, m), 6.69 (1H, s), 6.62 (1H, d, J 10 Hz), 4.29 (2H, q, J 7 Hz), 1.36 (3H, t, J 7 Hz). LCMS (ES^+) RT 3.56 minutes, 406 ($M+H$) $^+$.

20

EXAMPLE 16

Ethyl 3-[hydroxy(6-methylpyridin-2-yl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

25 A solution of Intermediate 5 (5.0 g, 13.0 mmol) in THF (500 ml) was cooled to -110°C under nitrogen and *n*-BuLi (6.4 ml of a 2.5M solution in hexanes, 16 mmol) was added slowly. A solution of 6-methyl-2-pyridinecarboxaldehyde (2.42 g, 20 mmol) in THF (5 ml) was added, the reaction mixture was warmed to -50°C and NaHCO₃(aq) (500 ml) added. The mixture was extracted with DCM (3 x 100 ml).
30 The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (20% EtOAc in DCM) to

give the *title compound* as a white solid (1.23 g, 42%). δ_{H} (CDCl_3) 7.82 (1H, d, J 9.8 Hz), 7.51-7.46 (4H, m), 7.29 (2H, br s), 7.02 (2H, t, J 7.0 Hz), 6.89 (1H, s), 6.41 (1H, d, J 9.8 Hz), 6.01 (1H, br s), 4.32-4.19 (2H, m), 2.57 (3H, s), 1.25 (3H, t, J 7.0 Hz). LCMS (ES^+) RT 2.87 minutes, 420.9 ($\text{M}+\text{H}$) $^+$.

5

EXAMPLE 17

Ethyl 3-[hydroxy(3-methylphenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

10 From Intermediate 5 and 3-methylbenzaldehyde by the method of Example 16. Light tan solid. δ_{H} (CDCl_3) 7.86 (1H, d, J 9.8 Hz), 7.56-7.47 (3H, m), 7.33 (2H, d, J 7.1 Hz), 7.18-7.11 (4H, m), 7.02 (1H, d, J 7.1 Hz), 6.57 (1H, s), 6.53 (1H, d, J 9.8 Hz), 4.20 (2H, q, J 7.1 Hz), 2.28 (3H, s), 1.21 (3H, t, J 7.1 Hz). LCMS (ES^+) RT 3.61 minutes, 420 ($\text{M}+\text{H}$) $^+$.

15

EXAMPLE 18

3-[Hydroxy(phenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

20 Intermediate 9 (520 mg, 1.57 mmol) was dissolved in THF (30 ml) and cooled to -100°C . *n*-BuLi (2.5M in hexanes, 0.75 ml, 1.9 mmol) was added dropwise with the internal temperature kept below -95°C . The red solution was stirred at -100°C for 30 min before the addition of a solution of benzaldehyde (0.24 ml, 2.4 mmol) in THF (10 ml). The reaction mixture was allowed to warm to room
25 temperature before addition of water (50 ml). The aqueous layer was extracted with DCM (2 x 100 ml) and the combined organic extracts dried (MgSO_4) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (10-20% EtOAc in DCM) to give the *title compound* as a white solid (140 mg, 25%). δ_{H} (CDCl_3) 7.90 (1H, d, J 9.8 Hz), 7.57-7.23 (10H, m), 6.52 (1H, d, J 9.8 Hz), 6.18
30 (1H, d, J 3.7 Hz), 2.89 (1H, br s). LCMS (ES^+) RT 3.24 minutes, 359 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 19**3-[Hydroxy(3-methylphenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carbonitrile**

- 5 From Intermediate 9 and 3-methylbenzaldehyde by the method of Example 18. White solid. δ_H (CDCl₃) 7.90 (1H, d, *J* 9.7 Hz), 7.55-7.45 (3H, m), 7.30-7.18 (5H, m), 7.05 (1H, m), 6.51 (1H, d, *J* 9.7 Hz), 6.13 (1H, d, *J* 3.2 Hz), 2.96 (1H, d, *J* 3.2 Hz), 2.11 (3H, s). LCMS (ES⁺) RT 3.38 minutes, 373 (M+H)⁺.

10

EXAMPLE 20**Ethyl 7-(cyclopropylmethyl)-3-[hydroxy(phenyl)methyl]-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate**

- A solution of Intermediate 13 (1.0 g, 2.81 mmol) and benzaldehyde (0.45 ml, 4.22 mmol) in anhydrous THF (100 ml) under nitrogen was cooled to -78°C. *tert*-Butyllithium (3.47 ml, 1.7M in pentane, 5.9 mmol) was added dropwise and the red solution allowed to stir at -78°C for one hour. The solution was allowed to warm to -10°C before the reaction was quenched by the addition of 10% aqueous ammonium chloride solution (250 ml). The mixture was extracted with DCM (3 x 100 ml), the organics washed with brine (2 x 200 ml), then dried (MgSO₄) and filtered, and the solvents removed *in vacuo*. The crude residue was purified by chromatography on silica (0-15% EtOAc in DCM) to give the *title compound* as an off-white solid (452 mg, 42%). δ_H (CDCl₃) 7.77 (1H, d, *J* 9.7 Hz), 7.34-7.32 (2H, m), 7.28-7.22 (2H, m), 7.20-7.17 (1H, m), 6.57 (1H, d, *J* 8.1 Hz), 6.44 (1H, d, *J* 9.7 Hz), 4.63 (1H, d, *J* 8.1 Hz), 4.33-4.22 (2H, m), 3.97 (2H, d, *J* 7.2 Hz), 1.35-1.28 (1H, m), 1.31 (3H, t, *J* 7.1 Hz), 0.54-0.48 (4H, m). LCMS (ES⁺) RT 3.59 minutes, 384 (M+H)⁺.
- 15
- 20
- 25

30

EXAMPLE 21**Ethyl 3-(anilinosulfonyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate**

- 5 A solution of Intermediate 5 (1.0 g, 2.65 mmol), in anhydrous THF (100 ml) under nitrogen was cooled to -78°C. *n*-Butyllithium (1.16 ml, 2.5M in hexanes, 2.91 mmol) was added dropwise and the red solution allowed to stir at -78°C for five minutes. Sulphur dioxide was bubbled through the reaction for 5 minutes at -78°C and the reaction then allowed to warm to room temperature. The volatiles were removed *in vacuo* and the crude residue suspended in DCM (50 ml). *N*-Chloro-
- 10 succinimide (425 mg, 3.18 mmol) was added and the reaction stirred at room temperature for two hours. Aniline (0.500 ml, 5.3 mmol), pyridine (2 ml) and DMAP (10 mg) were added and the reaction stirred for 18 hours. The reaction was diluted with DCM (150 ml) and washed with brine (3 x 200 ml). The organics were
- 15 dried (MgSO₄), filtered and the solvents removed *in vacuo*. The crude residue was purified by chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a white solid (320 mg, 27%). δ_H (CDCl₃) 8.65 (1H, br s), 8.44 (1H, d, *J* 10.0 Hz), 7.57-7.48 (3H, m), 7.30-7.25 (2H, m), 7.22-7.17 (2H, m), 7.12-7.06 (3H, m), 6.58 (1H, d, *J* 10.0 Hz), 4.33 (2H, q, *J* 7.1 Hz), 1.29 (3H, t, *J* 7.1 Hz). LCMS
- 20 (ES⁺) RT 3.59 minutes, 455 (M+H)⁺.

EXAMPLE 22**Ethyl 3-[(3-methylphenyl)thio]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-b]pyridine-2-carboxylate**

- 25 *m*-Thiocresol (1.99 ml, 16 mmol) was added to a suspension of sodium hydride (690 mg, 60% in mineral oil, 17.24 mmol) in DMF (50 ml) at -10°C and the mixture warmed to r.t. for 2 h. Intermediate 5 (5 g, 13.26 mmol) was added and the mixture stirred at r.t. for 2 h. The solvent was removed *in vacuo* and the residue
- 30 azeotroped with heptane (3 x 100 ml). Water (150 ml) was added and the mixture extracted with DCM (3 x 100 ml). The combined DCM extracts were washed with

brine, dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (silica, 100% DCM) gave the *title compound* as an off-white solid (4.2 g, 75%). δ_{H} (CDCl₃) 7.63-7.53 (4H, m), 7.45-7.42 (2H, m), 7.20-7.16 (2H, m), 7.10-7.03 (2H, m), 6.52 (1H, d, *J* 9.6 Hz), 4.30 (2H, q, *J* 7.1 Hz), 2.32 (3H, s), 1.29 (3H, t, *J* 7.1 Hz). LCMS (ES⁺) RT 4.11 minutes, 421.9 (M+H)⁺.

EXAMPLE 23

Ethyl 3-[2-(4-methylphenyl)hydrazino]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 5 (1.0 g, 2.6 mmol), tris(dibenzylideneacetone)-dipalladium(0) (0.24 g, 0.26 mmol) and BINAP (0.32 g, 0.52 mmol) in toluene (10 ml) was stirred under a nitrogen atmosphere for 10 minutes. *p*-Tolylhydrazine hydrochloride (0.5 g, 3.17 mmol), Cs₂CO₃ (2.06 g, 6.3 mmol) and toluene (5 ml) were added. The mixture was heated at 110°C overnight under a nitrogen atmosphere. The reaction was cooled to r.t., brine (50 ml) added and the aqueous extracted with EtOAc (2 x 50 ml). The combined EtOAc extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-10% EtOAc in DCM) to give the *title compound* as an orange solid (85 mg, 7.7%). δ_{H} (CDCl₃) 8.66 (1H, br s), 8.30 (1H, d, *J* 9.8 Hz), 7.55-7.32 (3H, m), 7.30 (2H, d, *J* 7.0 Hz), 7.02 (2H, d, *J* 8.2 Hz), 6.78 (2H, d, *J* 9.8 Hz), 6.37 (1H, d, *J* 9.8 Hz), 5.80 (1H, br s), 4.16 (2H, q, *J* 7.1 Hz), 2.22 (3H, s), 1.20 (3H, t, *J* 7.2 Hz). LCMS (ES⁺) RT 3.88 minutes, 420 (M+H)⁺.

EXAMPLE 24

Ethyl 3-[(3-chlorophenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 5 (5.0 g, 13 mmol) and 3-chlorobenzaldehyde (1.7 ml, 15 mmol) by the method of Example 16 to give 1.8 g (40%) of the *title compound*. δ_{H} (d₃-MeOD) 8.02 (1H, d, *J* 9.7 Hz), 7.48-7.38 (3H, m), 7.31 (1H, s), 7.23-7.16 (3H,

m), 7.10-7.00 (2H, m), 6.83 (1H, s), 6.29 (1H, d, J 9.7 Hz), 4.09 (2H, q, J 7.1 Hz), 1.07 (3H, t, J 7.1 Hz). LCMS (ES⁺) RT 3.70 minutes, 440 (M+H)⁺.

BIOLOGICAL ASSAYS

5

The following assays and animal models can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each assay an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition.

10

Preparation of activated human p38 α for inhibitor assays

Purification of human p38 α

Human p38 α , incorporating an *N*-terminal (His)₆ tag, was expressed in baculovirus-infected High-Five™ cells (Invitrogen) according to the manufacturer's instructions. The cells were harvested 72 h post-infection and lysed in phosphate-buffered saline (PBS) containing 1% (w/v) β -octylglucoside and Complete, EDTA-free™ protease inhibitors (Roche Molecular Biochemicals). The lysate was centrifuged at 35000 x g for 30 min at 4°C and the supernatant applied to a NiNTA™ column (Qiagen). Bound protein was eluted by 150 mM imidazole in PBS (after a wash with 15 mM imidazole in PBS) and directly applied to a HiTrap Q™ column (AP Biotech). Bound protein was eluted using a 20 column volume, 0 to 1 M NaCl gradient. Fractions containing (His)₆-p38 were aliquoted and stored at -70°C prior to their activation.

25 ***Preparation of GST-MKK6EE-containing lysates***

E. coli (BL21 pLysS) expressing the constitutively-activated form of human MKK6 fused with an *N*-terminal glutathione-*S*-transferase tag (GST-MKK6EE) were harvested by centrifugation and frozen at -70°C. Cells were lysed by resuspension in 1/10th the culture volume of PBS containing Complete, EDTA-free™ protease inhibitors followed by sonication on ice for 4 x 15 sec. Cell debris was removed by centrifugation at 35,000 x g and the resultant supernatant stored in aliquots at -70°C.

Activation of (His)6-p38

0.45 ml of purified (His)6-p38 was incubated with 50 µl of the GST-MKK6EE-containing lysate for 30 min at 23°C in the presence of 1 mM β-glycerophosphate, 10 mM MgCl₂ and 9 mM ATP. The extent of activation was monitored by mass spectrometric detection of the doubly-phosphorylated form of (His)6-p38, which routinely comprised greater than 90% of the final (His)6-p38 preparation. The activated (His)6-p38 was then diluted x 10 in PBS and repurified using the method described above. The concentration of purified, activated (His)6-p38 was measured by UV absorbance at 280 nm using A280, 0.1% = 1.2 and the preparation stored in aliquots at -70°C prior to its use in inhibitor assays.

p38 Inhibition Assays*Inhibition of phosphorylation of biotinylated myelin basic protein (MBP)*

The inhibition of p38-catalysed phosphorylation of biotinylated MBP is measured using a DELFIA-based format. The assay was performed in a buffer comprising 20 mM HEPES (pH 7.4), 5 mM MgCl₂ and 3 mM DTT. For a typical IC₅₀ determination, biotinylated MBP (2.5 µM) was incubated at room temperature in a streptavidin-coated microtitre plate together with activated gst-p38 (10 nM) and ATP (1 µM) in the presence of a range of inhibitor concentrations (final concentration of DMSO is 2 percent). After fifteen minutes the reaction was terminated by the addition of EDTA (75 mM). The microtitre plate was then washed with Tris-buffered saline (TBS), prior to the addition of 100 µl of anti-phospho MBP antibody (mouse) together with europium-labeled anti-mouse IgG antibody. After one hour at room temperature the plate was again washed in TBS followed by the addition of Enhancement solution (PerkinElmer Wallac). Fluorescence measurements were performed after a further fifteen minutes at room temperature. IC₅₀ values are determined from the plot of log₁₀[inhibitor concentration] (x-axis) versus percentage inhibition of the fluorescence generated by a control sample in the absence of inhibitor (y-axis).

Purification of human Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMC) were isolated from normal healthy volunteers. Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), diluted 1 in 4 in RPMI 1640 (Gibco, UK) and
5 centrifuged at 400 x g for 35 min over a Ficoll-paque gradient (Amersham-Pharmacia Biotech, UK). Cells at the interface were removed and washed once followed by a low speed spin (250 x g) to remove platelets. Cells were then resuspended in DMEM containing 10% FCS, penicillin 100 units ml⁻¹, streptomycin 50 µg ml⁻¹ and glutamine 2 mM (Gibco, UK).

10

Inhibitor dilutions

Inhibitor stocks (20 mM) were kept as a frozen solution (-20°C) in DMSO. Serial dilutions of inhibitors were performed in DMSO as 250-times concentrated stocks. Inhibitors were diluted 1 in 250 into tissue culture media, prewarmed to
15 37°C and transferred to plates containing PBMC. PBMC and inhibitors were incubated together for 30 min prior to addition of LPS. Inhibitors used in whole blood assays were prepared according to a different regime. Using the same stock solution serial dilutions of inhibitors were performed in DMSO. Inhibitors were then diluted 1 in 500 straight into whole blood in a volume of 1 µl. Inhibitor was
20 incubated with whole blood for 30 min prior to the addition of LPS.

LPS stimulation of PBMC

PBMC were resuspended at a density of 2 x 10⁵ cells/well in flat-bottomed 96-well tissue culture treated plates. After the addition of inhibitor cells were
25 stimulated with an optimal dose of LPS (*E. coli* strain B5:055, Sigma, at a final concentration of 1 µgml⁻¹) and incubated at 37°C in 5% CO₂/95% air for 18 hours. TNF-α levels were measured from cell-free supernatants by sandwich ELISA (BioSource #CHC1751).

30

LPS stimulation of whole blood

- Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), and 500 µl of blood aliquoted into each well of a 24-well tissue culture treated plate. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E. coli* strain B5:055, Sigma, at a final concentration of 1 µgml⁻¹) and incubated at 37°C without CO₂ for 18 hours. TNF-α levels were measured from cell-free supernatants by sandwich ELISA (BioSource #CHC1751).

Rat LPS-induced TNF release

- Male Lewis rats (180-200 g) are anaesthetised with Isofluror and injected i.v. with LPS* in a volume of 0.5 ml sterile saline. After 90 minutes blood is collected into EDTA tubes for preparation of plasma samples. Plasma is stored at -70°C prior to assay for TNF-α by commercial ELISA.

15 Rat CIA

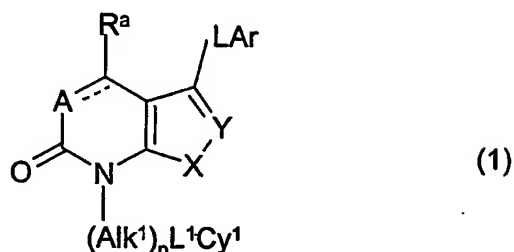
- Female Lewis rats (180-200 g) are anaesthetised with Isofluror and immunised i.d. at the base of the tail with 2 x 100 µl of emulsion containing 4 mg/ml bovine collagen II in 0.01 M acetic acid and Freund's Incomplete Adjuvant at a ratio of 1:1. A polyarthritis develops with onset from about 13 days post-sensitisation. The disease is mainly confined to the ankles and is quantified by plethysmometry. Results are expressed as change in paw volume over time.

Conclusion

- In the p38 inhibitor assays described above, the compounds of the Examples have IC₅₀ values of around 1 µM and below. The compounds of the invention are clearly potent inhibitors of p38 kinase, especially p38α kinase.

Claims:

1. A compound of formula (1):



5

wherein

the dashed line joining A and C(R^a) is present and represents a bond and A is a -N= atom or a -C(R^b)= group, or the dashed line is absent and A is a -N(R^b)- or

10 -C(R^b)(R^c)- group;

R^a, R^b and R^c is each independently a hydrogen atom or an optionally substituted C₁₋₆ alkyl, -CN, -CO₂H, -CO₂R¹ (where R¹ is an optionally substituted alkyl group), -CONH₂, -CONHR¹ or -CONR¹R² group (where R² is an optionally substituted alkyl group);

15 X is an -O-, -S- or substituted nitrogen atom or a -S(O)-, -S(O)₂- or -NH-group;

Y is a nitrogen or substituted carbon atom or a -CH= group;

n is zero or the integer 1;

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

20 L¹ is a covalent bond or a linker atom or group;

Cy¹ is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

L is an atom or chain -(CH₂)_pHet(CH₂)_q- in which p and q, which may be the same or different, is each zero or the integer 1 and Het is an -O- or -S- atom or a
25 -C(R^{3a})(R^{3b})- (where R^{3a} and R^{3b}, which may be the same or different, is each a

- hydrogen atom or an -OH or optionally substituted C₁₋₆ alkyl group), -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R^{3c})O- (where R^{3c} is a hydrogen atom or a straight or branched alkyl group), -N(R^{3c})NH-, -N(R^{3c})C(R^{3a})(R^{3b})-, -CON(R^{3c})-, -OC(O)N(R^{3c})-, -CSN(R^{3c})-, -N(R^{3c})CO-, -N(R^{3c})C(O)O-, -N(R^{3c})CS-,
- 5 -S(O)₂N(R^{3c})-, -N(R^{3c})S(O)₂-, -N(R^{3c})CON(R^{3d})- (where R^{3d} is as defined for R^{3c} and may be the same or different), -N(R^{3c})CSN(R^{3d})- or -N(R^{3c})S(O)₂N(R^{3d})- group and, when one or both of p and q is the integer 1, Het is additionally a -N(R^{3c})- group; and
- Ar is an optionally substituted aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof.

10

2. A compound as claimed in claim 1 wherein the dashed line joining A and C(R^a) is present and represents a bond and A is a -C(R^b)- group, in which R^a and R^b are as defined in claim 1.

15

3. A compound as claimed in claim 2 wherein R^a and R^b are both hydrogen.

4. A compound as claimed in any one of the previous claims wherein X is -S-.

20

5. A compound as claimed in any one of the previous claims wherein Y is -C(R¹⁰)= in which R¹⁰ is -CN, -CONH₂ or -CO₂Alk⁶ and Alk⁶ is C₁₋₄ alkyl.

6. A compound as claimed in any one of the previous claims wherein Cy¹ is phenyl or cyclopropyl.

25

7. A compound as claimed in any one of the previous claims wherein Ar represents phenyl, halophenyl, dihalophenyl, (C₁₋₆ alkyl)phenyl, pyridinyl or (C₁₋₆ alkyl)pyridinyl.

30

8. A compound as claimed in claim 1 as herein specifically disclosed in any one of the Examples.

9. A pharmaceutical composition comprising a compound of formula (1) as defined in claim 1, or a pharmaceutically acceptable salt, solvate, hydrate or *N*-oxide thereof, in association with a pharmaceutically acceptable carrier.

5

10. The use of a compound of formula (1) as defined in claim 1, or a pharmaceutically acceptable salt, solvate, hydrate or *N*-oxide thereof, for the manufacture of a medicament for the treatment and/or prevention of a disorder for which an inhibitor of p38 kinase is indicated.

10

11. A method for the treatment and/or prevention of a disorder for which an inhibitor of p38 kinase is indicated, which comprises administering to a patient in need of such treatment a compound of formula (1) as defined in claim 1, or a pharmaceutically acceptable salt, solvate, hydrate or *N*-oxide thereof.

15

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/03501

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04 A61K31/4365 A61P19/02 A61P29/00 A61P37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64400 A (BEMIS GUY ; VERTEX PHARMA (US); COCHRAN JOHN (US); SALITURO FRANCES) 16 December 1999 (1999-12-16) claim 1	1-10
X	US 6 169 092 B1 (BRAEUNLICH GABRIELE ET AL) 2 January 2001 (2001-01-02) claim 1	1-10
A	US 3 935 222 A (HOEHN HANS) 27 January 1976 (1976-01-27) claim 1	1-10
P,A	WO 03 033502 A (DAVIS JEREMY MARTIN ; BROOKINGS DANIEL CHRISTOPHER (GB); CELLTECH R) 24 April 2003 (2003-04-24) claim 1	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

16 December 2003

Date of mailing of the international search report

29/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax (+31-70) 340-3016

Authorized officer

Wolf, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/03501

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 03 03501

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 11

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB 03/03501

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9964400	A	16-12-1999	AU 4429799 A EP 1277740 A1 EP 1086085 A1 JP 2002517486 T WO 9964400 A1 US 2003149037 A1 US 2001025044 A1	30-12-1999 22-01-2003 28-03-2001 18-06-2002 16-12-1999 07-08-2003 27-09-2001
US 6169092	B1	02-01-2001	AU 3441197 A EP 0912578 A1 JP 2000514804 T WO 9802440 A1 ZA 9706168 A	09-02-1998 06-05-1999 07-11-2000 22-01-1998 02-02-1998
US 3935222	A	27-01-1976	NONE	
WO 03033502	A	24-04-2003	WO 03033502 A1	24-04-2003